

THERAPEUTIC AGENTS USEFUL FOR TREATING PAIN

This application claims the benefit of U.S. Provisional Application No. 60/416,525, filed October 8, 2002; U.S. Provisional Application No. 60/413,155, filed September 25, 2002; U.S. Provisional Application No. 60/411,020, filed September 17, 2002; and U.S. Provisional Application No. 60/398,594, filed July 26, 2002, each of which
5 is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

The present invention relates to Pyridazinylpiperazine Compounds, compositions comprising an effective amount of a Pyridazinylpiperazine Compound and methods for treating or preventing pain, urinary incontinence (UI), an ulcer, inflammatory-
10 bowel disease (IBD), irritable-bowel syndrome (IBS), an addictive disorder, Parkinson's disease, parkinsonism, anxiety, epilepsy, stroke, a seizure, a pruritic condition, psychosis, a cognitive disorder, a memory deficit, restricted brain function, Huntington's chorea, amyotrophic lateral sclerosis (ALS), dementia, retinopathy, a muscle spasm, a migraine, vomiting, dyskinesia or depression, comprising administering to an animal in need thereof
15 an effective amount of a Pyridazinylpiperazine Compound.

1. BACKGROUND OF THE INVENTION

Pain is the most common symptom for which patients seek medical advice and treatment. Pain can be acute or chronic. While acute pain is usually self-limited, chronic pain persists for 3 months or longer and can lead to significant changes in a patient's
20 personality, lifestyle, functional ability and overall quality of life (K.M. Foley, *Pain*, in *Cecil Textbook of Medicine* 100-107 (J.C. Bennett and F. Plum eds., 20th ed. 1996)).

Moreover, chronic pain can be classified as either nociceptive or neuropathic. Nociceptive pain includes tissue injury-induced pain and inflammatory pain such as that associated with arthritis. Neuropathic pain is caused by damage to the peripheral or central
25 nervous system and is maintained by aberrant somatosensory processing. There is a large body of evidence relating activity at both Group I mGluRs (mGluR1 and mGluR5) (M.E. Fundytus, *CNS Drugs* 15:29-58 (2001)) and vanilloid receptors (VR1) (V. Di Marzo *et al.*, *Current Opinion in Neurobiology* 12:372-379 (2002)) to pain processing. Inhibiting mGluR1 or mGluR5 reduces pain, as shown by *in vivo* treatment with antibodies selective
30 for either mGluR1 or mGluR5, where neuropathic pain in rats was attenuated (M.E. Fundytus *et al.*, *NeuroReport* 9:731-735 (1998)). It has also been shown that antisense oligonucleotide knockdown of mGluR1 alleviates both neuropathic and inflammatory pain

(M.E. Fundytus *et al.*, *British Journal of Pharmacology* 132:354-367 (2001); M.E. Fundytus *et al.*, *Pharmacology, Biochemistry & Behavior* 73:401-410 (2002)). Small molecule antagonists for mGluR5-attenuated pain in *in vivo* animal models are disclosed in, e.g., K. Walker *et al.*, *Neuropharmacology* 40:1-9 (2000) and A. Dogrul *et al.*,
5 *Neuroscience Letters* 292:115-118 (2000)).

Nociceptive pain has been traditionally managed by administering non-opioid analgesics, such as acetylsalicylic acid, choline magnesium trisalicylate, acetaminophen, ibuprofen, fenoprofen, diflusal, and naproxen; or opioid analgesics, including morphine, hydromorphone, methadone, levorphanol, fentanyl, oxycodone, and oxymorphone. *Id.* In
10 addition to the above-listed treatments, neuropathic pain, which can be difficult to treat, has also been treated with anti-epileptics (e.g. gabapentin, carbamazepine, valproic acid, topiramate, phenytoin), NMDA antagonists (e.g. ketamine, dextromethorphan), topical lidocaine (for post-herpetic neuralgia), and tricyclic antidepressants (e.g. fluoxetine, sertraline and amitriptyline).

15 Pain has been traditionally managed by administering non-opioid analgesics, such as acetylsalicylic acid, choline magnesium trisalicylate, acetaminophen, ibuprofen, fenoprofen, diflusal, and naproxen; or opioid analgesics, including morphine, hydromorphone, methadone, levorphanol, fentanyl, oxycodone, and oxymorphone. *Id.*

Urinary incontinence ("UI") is uncontrollable urination, generally caused by
20 bladder-detrusor-muscle instability. UI affects people of all ages and levels of physical health, both in health care settings and in the community at large. At present, UI afflicts 15-30% of elderly people living at home, one-third of those living in acute-care settings, and at least one-half of those living in long-term care institutions (R.M. Resnick, *Lancet* 346:94 (1995)). Persons having UI are predisposed to also having urinary-tract infections, pressure
25 ulcers, perineal rashes and urosepsis. Psychosocially, UI is associated with embarrassment, social stigmatization, depression and a risk of institutionalization (Herzo *et al.*, *Annu. Rev. Gerontol. Geriatr.* 9:74 (1989)). Economically, the costs of UI are great; in the United States alone, health-care costs associated with UI are over \$15 billion per annum.

Physiologic bladder contraction results in large part from acetylcholine-induced
30 stimulation of post-ganglionic muscarinic-receptor sites on bladder smooth muscle. Treatments for UI include the administration of drugs having bladder-relaxant properties, which help to control bladder-detrusor-muscle overactivity. For example, anticholinergics such as propantheline bromide and glycopyrrolate, and combinations of smooth-muscle relaxants such as a combination of racemic oxybutynin and dicyclomine or an

anticholinergic, have been used to treat UI (See, e.g., A.J. Wein, *Urol. Clin. N. Am.* 22:557-577 (1995); Levin *et al.*, *J. Urol.* 128:396-398 (1982); Cooke *et al.*, *S. Afr. Med. J.* 63:3 (1983); R.K. Mirakhur *et al.*, *Anaesthesia* 38:1195-1204 (1983)). These drugs are not effective, however, in all patients having uninhibited bladder contractions. Administration
5 of anticholinergic medications represent the mainstay of this type of treatment.

None of the existing commercial drug treatments for UI has achieved complete success in all classes of UI patients, nor has treatment occurred without significant adverse side effects. For example, drowsiness, dry mouth, constipation, blurred vision, headaches, tachycardia, and cardiac arrhythmia, which are related to the anticholinergic activity of
10 traditional anti-UI drugs, can occur frequently and adversely affect patient compliance. Yet despite the prevalence of unwanted anticholinergic effects in many patients, anticholinergic drugs are currently prescribed for patients having UI. *The Merck Manual of Medical Information* 631-634 (R. Berkow ed., 1997).

Ulcers are sores occurring where the lining of the digestive tract has been eroded by
15 stomach acids or digestive juices. The sores are typically well-defined round or oval lesions primarily occurring in the stomach and duodenum. About 1 in 10 people develop an ulcer. Ulcers develop as a result of an imbalance between acid-secretory factors, also known as “aggressive factors,” such as stomach acid, pepsin, and *Helicobacter pylori* infection, and local mucosal-protective factors, such as secretion of bicarbonate, mucus, and
20 prostaglandins.

Treatment of ulcers typically involves reducing or inhibiting the aggressive factors. For example, antacids such as aluminum hydroxide, magnesium hydroxide, sodium bicarbonate, and calcium bicarbonate can be used to neutralize stomach acids. Antacids, however, can cause alkalosis, leading to nausea, headache, and weakness. Antacids can
25 also interfere with the absorption of other drugs into the blood stream and cause diarrhea.

H₂ antagonists, such as cimetidine, ranitidine, famotidine, and nizatidine, are also used to treat ulcers. H₂ antagonists promote ulcer healing by reducing gastric acid and digestive-enzyme secretion elicited by histamine and other H₂ agonists in the stomach and duodenum. H₂ antagonists, however, can cause breast enlargement and impotence in men,
30 mental changes (especially in the elderly), headache, dizziness, nausea, myalgia, diarrhea, rash, and fever.

H⁺, K⁺ - ATPase inhibitors such as omeprazole and lansoprazole are also used to treat ulcers. H⁺, K⁺ - ATPase inhibitors inhibit the production of enzymes used by the stomach to secrete acid. Side effects associated with H⁺, K⁺ - ATPase inhibitors include

nausea, diarrhea, abdominal colic, headache, dizziness, somnolence, skin rashes, and transient elevations of plasma activities of aminotransferases.

Sucraflate is also used to treat ulcers. Sucraflate adheres to epithelial cells and is believed to form a protective coating at the base of an ulcer to promote healing. Sucraflate, however, can cause constipation, dry mouth, and interfere with the absorption of other drugs.

Antibiotics are used when *Helicobacter pylori* is the underlying cause of the ulcer. Often antibiotic therapy is coupled with the administration of bismuth compounds such as bismuth subsalicylate and colloidal bismuth citrate. The bismuth compounds are believed to enhance secretion of mucous and HCO_3^- , inhibit pepsin activity, and act as an antibacterial against *H. pylori*. Ingestion of bismuth compounds, however, can lead to elevated plasma concentrations of Bi^{+3} and can interfere with the absorption of other drugs.

Prostaglandin analogues, such as misoprostal, inhibit secretion of acid and stimulate the secretion of mucous and bicarbonate and are also used to treat ulcers, especially ulcers in patients who require nonsteroidal anti-inflammatory drugs. Effective oral doses of prostaglandin analogues, however, can cause diarrhea and abdominal cramping. In addition, some prostaglandin analogues are abortifacients.

Carbenoxolone, a mineral corticoid, can also be used to treat ulcers. Carbenoxolone appears to alter the composition and quantity of mucous, thereby enhancing the mucosal barrier. Carbenoxolone, however, can lead to Na^+ and fluid retention, hypertension, hypokalemia, and impaired glucose tolerance.

Muscarinic cholinergic antagonists such as pirenzapine and telenzapine can also be used to reduce acid secretion and treat ulcers. Side effects of muscarinic cholinergic antagonists include dry mouth, blurred vision, and constipation. *The Merck Manual of Medical Information* 496-500 (R. Berkow ed., 1997) and *Goodman and Gilman's The Pharmacological Basis of Therapeutics* 901-915 (J. Hardman and L. Limbird eds., 9th ed. 1996).

Irritable-bowel disease ("IBD") is a chronic disorder in which the bowel becomes inflamed, often causing recurring abdominal cramps and diarrhea. The two types of IBD are Crohn's disease and ulcerative colitis.

Crohn's disease, which can include regional enteritis, granulomatous ileitis, and ileocolitis, is a chronic inflammation of the intestinal wall. Crohn's disease occurs equally in both sexes and is more common in Jews of eastern-European ancestry. Most cases of

Crohn's disease begin before age 30 and the majority start between the ages of 14 and 24. The disease typically affects the full thickness of the intestinal wall. Generally the disease affects the lowest portion of the small intestine (ileum) and the large intestine, but can occur in any part of the digestive tract.

5 Early symptoms of Crohn's disease are chronic diarrhea, crampy abdominal pain, fever, loss of appetite, and weight loss. Complications associated with Crohn's disease include the development of intestinal obstructions, abnormal connecting channels (fistulas), and abscesses. The risk of cancer of the large intestine is increased in people who have Crohn's disease. Often Crohn's disease is associated with other disorders such as
10 gallstones, inadequate absorption of nutrients, amyloidosis, arthritis, episcleritis, aphthous stomatitis, erythema nodosum, pyoderma gangrenosum, ankylosing spondylitis, sacroilitis, uveitis, and primary sclerosing cholangitis. There is no known cure for Crohn's disease.

 Cramps and diarrhea, side effects associated with Crohn's disease, can be relieved by anticholinergic drugs, diphenoxylate, loperamide, deodorized opium tincture, or codeine.
15 Generally, the drug is taken orally before a meal.

 Broad-spectrum antibiotics are often administered to treat the symptoms of Crohn's disease. The antibiotic metronidazole is often administered when the disease affects the large intestine or causes abscesses and fistulas around the anus. Long-term use of metronidazole, however, can damage nerves, resulting in pins-and-needles sensations in the
20 arms and legs. Sulfasalazine and chemically related drugs can suppress mild inflammation, especially in the large intestine. These drugs, however, are less effective in sudden, severe flare-ups. Corticosteroids, such as prednisone, reduce fever and diarrhea and relieve abdominal pain and tenderness. Long-term corticosteroid therapy, however, invariably results in serious side effects such as high blood-sugar levels, increased risk of infection,
25 osteoporosis, water retention, and fragility of the skin. Drugs such as azathioprine and mercaptopurine can compromise the immune system and are often effective for Crohn's disease in patients that do not respond to other drugs. These drugs, however, usually need 3 to 6 months before they produce benefits and can cause serious side effects such as allergy, pancreatitis, and low white-blood-cell count.

30 When Crohn's disease causes the intestine to be obstructed or when abscesses or fistulas do not heal, surgery can be necessary to remove diseased sections of the intestine. Surgery, however, does not cure the disease, and inflammation tends to recur where the intestine is rejoined. In almost half of the cases a second operation is needed. *The Merck Manual of Medical Information* 528-530 (R. Berkow ed., 1997).

Ulcerative colitis is a chronic disease in which the large intestine becomes inflamed and ulcerated, leading to episodes of bloody diarrhea, abdominal cramps, and fever.

Ulcerative colitis usually begins between ages 15 and 30; however, a small group of people have their first attack between ages 50 and 70. Unlike Crohn's disease, ulcerative colitis never affects the small intestine and does not affect the full thickness of the intestine. The disease usually begins in the rectum and the sigmoid colon and eventually spreads partially or completely throughout the large intestine. The cause of ulcerative colitis is unknown.

Treatment of ulcerative colitis is directed to controlling inflammation, reducing symptoms, and replacing lost fluids and nutrients. Anticholinergic drugs and low doses of diphenoxylate or loperamide are administered for treating mild diarrhea. For more intense diarrhea higher doses of diphenoxylate or loperamide, or deodorized opium tincture or codeine are administered. Sulfasalazine, olsalazine, prednisone, or mesalamine can be used to reduce inflammation. Azathioprine and mercaptopurine have been used to maintain remissions in ulcerative-colitis patients who would otherwise need long-term corticosteroid treatment. In severe cases of ulcerative colitis the patient is hospitalized and given corticosteroids intravenously. People with severe rectal bleeding can require transfusions and intravenous fluids. If toxic colitis develops and treatments fail, surgery to remove the large intestine can be necessary. Non-emergency surgery can be performed if cancer is diagnosed, precancerous lesions are detected, or unremitting chronic disease would otherwise make the person an invalid or dependent on high doses of corticosteroids. Complete removal of the large intestine and rectum permanently cures ulcerative colitis. *The Merck Manual of Medical Information* 530-532 (R. Berkow ed., 1997) and *Goodman and Gilman's The Pharmacological Basis of Therapeutics* (J. Hardman and L. Limbird eds., 9th ed. 1996).

Inflammatory-bowel syndrome ("IBS") is a disorder of motility of the entire gastrointestinal tract, causing abdominal pain, constipation, and/or diarrhea. IBS affects three-times more women than men. In IBS stimuli such as stress, diet, drugs, hormones, or irritants can cause the gastrointestinal tract to contract abnormally. During an episode of IBS, contractions of the gastrointestinal tract become stronger and more frequent, resulting in the rapid transit of food and feces through the small intestine, often leading to diarrhea. Cramps result from the strong contractions of the large intestine and increased sensitivity of pain receptors in the large intestine.

There are two major types of IBS. The first type, spastic-colon type, is commonly triggered by eating, and usually produces periodic constipation and diarrhea with pain.

Mucous often appears in the stool. The pain can come in bouts of continuous dull aching pain or cramps, usually in the lower abdomen. The person suffering from spastic-colon type IBS can also experience bloating, gas, nausea, headache, fatigue, depression, anxiety, and difficulty concentrating. The second type of IBS usually produces painless diarrhea or constipation. The diarrhea can begin suddenly and with extreme urgency. Often the diarrhea occurs soon after a meal and can sometimes occur immediately upon awakening.

Treatment of IBS typically involves modification of an IBS-patient's diet. Often it is recommended that an IBS patient avoid beans, cabbage, sorbitol, and fructose. A low-fat, high-fiber diet can also help some IBS patients. Regular physical activity can also help keep the gastrointestinal tract functioning properly. Drugs such as propantheline that slow the function of the gastrointestinal tract are generally not effective for treating IBS. Antidiarrheal drugs, such as diphenoxylate and loperamide, help with diarrhea. *The Merck Manual of Medical Information* 525-526 (R. Berkow ed., 1997).

Many drugs can cause physical and/or psychological addiction. Those most well known types of these drugs include opiates, such as heroin, opium, and morphine; sympathomimetics, including cocaine and amphetamines; sedative-hypnotics, including alcohol, benzodiazepines and barbiturates; and nicotine, which has effects similar to opioids and sympathomimetics. Drug addiction is characterized by a craving or compulsion for taking the drug and an inability to limit its intake. Additionally, drug dependence is associated with drug tolerance, the loss of effect of the drug following repeated administration, and withdrawal, the appearance of physical and behavioral symptoms when the drug is not consumed. Sensitization occurs if repeated administration of a drug leads to an increased response to each dose. Tolerance, sensitization, and withdrawal are phenomena evidencing a change in the central nervous system resulting from continued use of the drug. This change can motivate the addicted individual to continue consuming the drug despite serious social, legal, physical and/or professional consequences. (See, e.g., U.S. Patent No. 6,109,269 to Rise *et al.*).

Certain pharmaceutical agents have been administered for treating addiction. U.S. Patent No. 5,556,838 to Mayer *et al.* discloses the use of nontoxic NMDA-blocking agents co-administered with an addictive substance to prevent the development of tolerance or withdrawal symptoms. U.S. Patent No. 5,574,052 to Rose *et al.* discloses co-administration of an addictive substance with an antagonist to partially block the pharmacological effects of the addictive substance. U.S. Patent No. 5,075,341 to Mendelson *et al.* discloses the use of a mixed opiate agonist/antagonist to treat cocaine and opiate addiction. U.S. Patent No.

5,232,934 to Downs discloses administration of 3-phenoxypyridine to treat addiction. U.S. Patents No. 5,039,680 and 5,198,459 to Imperato *et al.* disclose using a serotonin antagonist to treat chemical addiction. U.S. Patent No. 5,556,837 to Nestler *et. al.* discloses infusing BDNF or NT-4 growth factors to inhibit or reverse neurological adaptive changes that
5 correlate with behavioral changes in an addicted individual. U.S. Patent. No. 5,762,925 to Sagan discloses implanting encapsulated adrenal medullary cells into an animal's central nervous system to inhibit the development of opioid intolerance. U.S. Patent No. 6,204,284 to Beer *et al.* discloses racemic (\pm)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane for use in the prevention or relief of a withdrawal syndrome resulting from addiction to drugs
10 and for the treatment of chemical dependencies.

Parkinson's disease is a clinical syndrome comprising bradykinesia (slowness and poverty of movement), muscular rigidity, resting tremor (which usually abates during voluntary movement), and an impairment of postural balance leading to disturbance of gait and falling. The features of Parkinson's disease are a loss of pigmented, dopaminergic
15 neurons of the substantia nigra pars compacta and the appearance of intracellular inclusions known as Lewy bodies (*Goodman and Gillman's The Pharmaceutical Basis of Therapeutics* 506 (9th ed. 1996)). Without treatment, Parkinson's disease progresses to a rigid akinetic state in which patients are incapable of caring for themselves. Death frequently results from complications of immobility, including aspiration pneumonia or
20 pulmonary embolism. Drugs commonly used for the treatment of Parkinson's disease include carbidopa/levodopa, pergolide, bromocriptine, selegiline, amantadine, and trihexyphenidyl hydrochloride. There remains, however, a need for drugs useful for the treatment of Parkinson's disease and having an improved therapeutic profile.

Anxiety is a fear, apprehension, or dread of impending danger often accompanied by
25 restlessness, tension, tachycardia, and dyspnea. Other symptoms commonly associated with anxiety include depression, especially accompanied with dysthymic disorder (chronic "neurotic" depression); panic disorder; agoraphobia and other specific phobias; eating disorders; and many personality disorders. Often anxiety is unattached to a clearly identified treatable primary illness. If a primary illness is found, however, it can be
30 desirable to deal with the anxiety at the same time as the primary illness.

Currently, benzodiazepines are the most commonly used anti-anxiety agents for generalized anxiety disorder. Benzodiazepines, however, carry the risk of producing impairment of cognition and skilled motor functions, particularly in the elderly, which can result in confusion, delirium, and falls with fractures. Sedatives are also commonly

prescribed for treating anxiety. The azapirones, such as buspirone, are also used to treat moderate anxiety. The azapirones, however, are less useful for treating severe anxiety accompanied with panic attacks.

5 Epilepsy is a disorder characterized by the tendency to have recurring seizures. The
etiology commonly consists of lesions in some part of the cortex, such as a tumor;
developmental malformation; or damage due to trauma or stroke. In some cases the
etiology is genetic. An epileptic seizure can be triggered by repetitive sounds, flashing
lights, video games, or touching certain parts of the body. Epilepsy is typically treated with
anti-seizure drugs. In epilepsy cases, where anti-seizure drugs are ineffective, and the
10 defect in the brain is isolated to a small area of the brain, surgical removal of that part of the
brain can be helpful in alleviating the seizures. In patients who have several sources for the
seizures or who have seizures that spread quickly to all parts of the brain, surgical removal
of the nerve fibers that connect the two sides of the brain can be helpful.

 Examples of drugs for treating a seizure and epilepsy include carbamazepine,
15 ethosuximide, gabapentin, lamotrigine, phenobarbital, phenytoin, primidone, valproic acid,
trimethadione, benzodiazepines, γ -vinyl GABA, acetazolamide, and felbamate. Anti-
seizure drugs, however, can have side effects such as drowsiness; hyperactivity;
hallucinations; inability to concentrate; central and peripheral nervous system toxicity, such
as nystagmus, ataxia, diplopia, and vertigo; gingival hyperplasia; gastrointestinal
20 disturbances such as nausea, vomiting, epigastric pain, and anorexia; endocrine effects such
as inhibition of antidiuretic hormone, hyperglycemia, glycosuria, osteomalacia; and
hypersensitivity such as scarlatiniform rash, morbilliform rash, Stevens-Johnson syndrome,
systemic lupus erythematosus, and hepatic necrosis; and hematological reactions such as
red-cell aplasia, agranulocytosis, thrombocytopenia, aplastic anemia, and megaloblastic
25 anemia. *The Merck Manual of Medical Information* 345-350 (R. Berkow ed., 1997).

 A seizure is the result of abnormal electrical discharge in the brain. The discharge
can involve a small area of the brain and lead to the person only noticing an odd taste or
smell or it can involve a large area of the brain and lead to convulsions, *i.e.*, a seizure that
causes jerking and spasms of the muscles throughout the body. Convulsions can also result
30 in brief attacks of altered consciousness and loss of consciousness, muscle control, or
bladder control. A seizures is often preceded by auras, *i.e.*, unusual sensations of smell,
taste, or vision or an intense feeling that a seizure is about to begin. A seizure typically lasts
for about 2 to 5 minutes. When the seizure ends the person can have headache, sore

muscles, unusual sensations, confusion, and profound fatigue (postictal state). Usually the person cannot remember what happened during the seizure.

5 A stroke or cerebrovascular accident, is the death of brain tissue (cerebral infarction) resulting from the lack of blood flow and insufficient oxygen to the brain. A stroke can be either ischemic or hemorrhagic. In an ischemic stroke, blood supply to the brain is cut off because of atherosclerosis or a blood clot that has blocked a blood vessel. In a hemorrhagic stroke, a blood vessel bursts preventing normal blood flow and allowing blood to leak into an area of the brain and destroying it. Most strokes develop rapidly and cause brain damage within minutes. In some cases, however, strokes can continue to worsen for several hours or days. Symptoms of strokes vary depending on what part of the brain is effected. Symptoms include loss or abnormal sensations in an arm or leg or one side of the body, weakness or paralysis of an arm or leg or one side of the body, partial loss of vision or hearing, double vision, dizziness, slurred speech, difficulty in thinking of the appropriate word or saying it, inability to recognize parts of the body, unusual movements, loss of bladder control, imbalance, and falling, and fainting. The symptoms can be permanent and can be associated with coma or stupor. Strokes can cause edema or swelling of the brain which can further damage brain tissue. For persons suffering from a stroke, intensive rehabilitation can help overcome the disability caused by impairment of brain tissue. Rehabilitation trains other parts of the brain to assume the tasks previously performed by the damaged part.

Examples of drugs for treating strokes include anticoagulants such as heparin, drugs that break up clots such as streptokinase or tissue plasminogen activator, and drugs that reduce swelling such as mannitol or corticosteroids. *The Merck Manual of Medical Information* 352-355 (R. Berkow ed., 1997).

25 Pruritus is an unpleasant sensation that prompts scratching. Pruritus can be attributed to dry skin, scabies, dermatitis, herpetiformis, atopic dermatitis, *pruritus vulvae et ani*, miliaria, insect bites, pediculosis, contact dermatitis, drug reactions, urticaria, urticarial eruptions of pregnancy, psoriasis, lichen planus, lichen simplex chronicus, exfoliative dermatitis, folliculitis, bullous pemphigoid, and fiberglass dermatitis. Conventionally, pruritus is treated by phototherapy with ultraviolet B or PUVA or with therapeutic agents such as naltrexone, nalmeferene, danazol, tricyclics, and antidepressants.

Selective antagonists of the metabotropic glutamate receptor 5 ("mGluR5") have been shown to exert analgesic activity in *in vivo* animal models (K. Walker *et al.*,

Neuropharmacology 40:1-9 (2000) and A. Dogrul *et al.*, *Neuroscience Letters*, 292(2):115-118 (2000)).

5 Selective antagonists of the mGluR5 receptor have also been shown to exert anxiolytic and anti-depressant activity in *in vivo* animal models (E. Tatarczynska *et al.*, *Br. J. Pharmacol.* 132(7):1423-1430 (2001) and P.J.M. Will *et al.*, *Trends in Pharmacological Sciences* 22(7):331-37 (2001)).

Selective antagonists of the mGluR5 receptor have also been shown to exert anti-Parkinson activity *in vivo* (K. J. Ossowska *et al.*, *Neuropharmacology* 41(4):413-20 (2001) and P.J.M. Will *et al.*, *Trends in Pharmacological Sciences* 22(7):331-37 (2001)).

10 Selective antagonists of the mGluR5 receptor have also been shown to exert anti-dependence activity *in vivo* (C. Chiamulera *et al.*, *Nature Neuroscience* 4(9):873-74 (2001)).

U.S. Patent No. 5,607,936 to Chiang *et al.* discloses a class of aryl piperazine compounds allegedly useful for treating inflammatory diseases, pain, or migraine.

15 International publication no. WO 00/42852 discloses a class of substituted heterocyclic compounds allegedly useful as modulators, agonists, or antagonists of the CCR5 receptor.

European patent publication no. EP 1 122 242 discloses cyanophenyl and nitrophenyl compounds allegedly having antiandrogen activity.

20 International publication no. WO 02/06234 discloses a class of sulfone compounds allegedly useful as blood anti-coagulants.

Japanese patent application no. 10-7572 discloses substituted piperazine compounds that allegedly are inhibitors of tumor necrosis factor.

25 International publication no. WO 02/074743 discloses aryl substituted alicyclic compounds that allegedly inhibit $\alpha v \beta 3$ integrin.

Japanese patent application no. 2001-328938 discloses cyanophenyl derivatives that allegedly have anti-androgen activity and are useful for the treatment of prostate cancer and prostate hypertrophy.

30 Japanese patent application no. 2001-261657 discloses cyanophenyl derivatives that allegedly have anti-androgen activity.

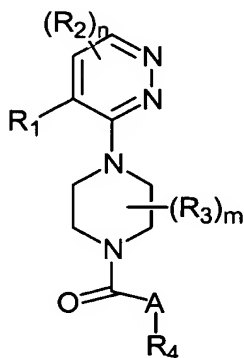
There remains, however, a clear need in the art for new drugs useful for treating or preventing pain, UI, an ulcer, IBD, IBS, an addictive disorder, Parkinson's

disease, parkinsonism, anxiety, epilepsy, stroke, a seizure, a pruritic condition, psychosis, a cognitive disorder, a memory deficit, restricted brain function, Huntington's chorea, ALS, dementia, retinopathy, a muscle spasm, a migraine, vomiting, dyskinesia, or depression.

Citation of any reference in Section 2 of this application is not to be
5 construed as an admission that such reference is prior art to the present application.

2. SUMMARY OF THE INVENTION

The present invention encompasses compounds having the formula (I):



10 (I)
and pharmaceutically acceptable salts thereof, wherein:

A is -NH-, -N(C₁-C₆)alkyl-, or -N-(O-C₁-C₆ alkyl)-;

R₁ is -halo, -CH₃, -NO₂, -CN, -OH, -OCH₃, -NH₂, C(halo)₃, -CH(halo)₂, or -CH₂(halo);

15 each R₂ is independently:

(a) -halo, -OH, or -NH₂;

(b) -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or
20 more R₅ groups; or

(c) -phenyl, -naphthyl, -(C₁₄)aryl or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R₆ groups;

each R₃ is independently:

25 (a) -halo, -CN, -OH, -NO₂, or -NH₂;

(b) $-(C_1-C_{10})$ alkyl, $-(C_2-C_{10})$ alkenyl, $-(C_2-C_{10})$ alkynyl, $-(C_3-C_{10})$ cycloalkyl, $-(C_8-C_{14})$ bicycloalkyl, $-(C_8-C_{14})$ tricycloalkyl, $-(C_5-C_{10})$ cycloalkenyl, $-(C_8-C_{14})$ bicycloalkenyl, $-(C_8-C_{14})$ tricycloalkenyl, $-(3- \text{ to } 7\text{-membered})$ heterocycle, or $-(7- \text{ to } 10\text{-membered})$ bicycloheterocycle, each of which is unsubstituted or substituted with one or
5 more R_5 groups; or

(c) -phenyl, -naphthyl, $-(C_{14})$ aryl or $-(5- \text{ to } 10\text{-membered})$ heteroaryl, each of which is unsubstituted or substituted with one or more R_6 groups;

R_4 is:

(a) $-(C_1-C_{10})$ alkyl, $-(C_2-C_{10})$ alkenyl, $-(C_2-C_{10})$ alkynyl, $-(C_3-C_{10})$ cycloalkyl, $-(C_8-C_{14})$ bicycloalkyl, $-(C_8-C_{14})$ tricycloalkyl, $-(C_5-C_{10})$ cycloalkenyl, $-(C_8-C_{14})$ bicycloalkenyl, $-(C_8-C_{14})$ tricycloalkenyl, $-(3- \text{ to } 7\text{-membered})$ heterocycle, or $-(7- \text{ to } 10\text{-membered})$ bicycloheterocycle, each of which is unsubstituted or substituted with one or
10 more R_5 groups; or

(b) -phenyl, -naphthyl, $-(C_{14})$ aryl or $-(5- \text{ to } 10\text{-membered})$ heteroaryl, each of which is unsubstituted or substituted with one or more R_6 groups;
15

each R_5 is independently -CN, -OH, $-(C_1-C_6)$ alkyl, $-(C_2-C_6)$ alkenyl, -halo, $-N_3$, $-NO_2$, $-N(R_7)_2$, $-CH=NR_7$, $-NR_7OH$, $-OR_7$, $-COR_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-OC(O)OR_7$, $-SR_7$, $-S(O)R_7$, or $-S(O)_2R_7$;

each R_6 is independently $-(C_1-C_6)$ alkyl, $-(C_2-C_6)$ alkenyl, $-(C_2-C_6)$ alkynyl, $-(C_3-C_8)$ cycloalkyl, $-(C_5-C_8)$ cycloalkenyl, -phenyl, $-(3- \text{ to } 5\text{-membered})$ heterocycle, $-C(halo)_3$, $-CH(halo)_2$, $-CH_2(halo)$, -CN, -OH, -halo, $-N_3$, $-NO_2$, $-N(R_7)_2$, $-CH=NR_7$, $-NR_7OH$, $-OR_7$, $-COR_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-OC(O)OR_7$, $-SR_7$, $-S(O)R_7$, or $-S(O)_2R_7$;
20

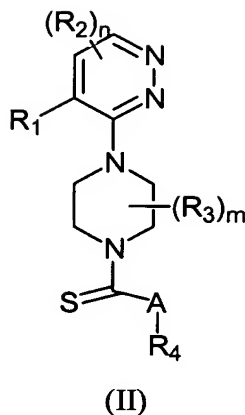
each R_7 is independently -H, $-(C_1-C_6)$ alkyl, $-(C_2-C_6)$ alkenyl, $-(C_2-C_6)$ alkynyl, $-(C_3-C_8)$ cycloalkyl, $-(C_5-C_8)$ cycloalkenyl, -phenyl, $-(3- \text{ to } 5\text{-membered})$ heterocycle, $-C(halo)_3$, $-CH(halo)_2$, or $-CH_2(halo)$;
25

each halo is independently -F, -Cl, -Br, or -I;

n is an integer ranging from 0 to 2; and

m is an integer ranging from 0 to 2.

The present invention encompasses compounds having the formula (II):



and pharmaceutically acceptable salts thereof, wherein:

A is -N(O-C₁-C₆ alkyl)-, -CH₂-, -CH₂CH₂-, or -CH=CH-;

5 R₁ is -halo, -CH₃, -NO₂, -CN, -OH, -OCH₃, -NH₂, C(halo)₃, -CH(halo)₂, or -CH₂(halo);

each R₂ is independently:

(a) -halo, -CN, -OH, -NO₂, or -NH₂;

(b) -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-
 10 C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R₅ groups; or

(c) -phenyl, -naphthyl, -(C₁₄)aryl or -(5- to 10-membered)heteroaryl,
 15 each of which is unsubstituted or substituted with one or more R₆ groups;

each R₃ is independently:

(a) -halo, -CN, -OH, -NO₂, or -NH₂;

(b) -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-
 C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-C₁₀)cycloalkenyl, -(C₈-
 20 C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R₅ groups; or

(c) -phenyl, -naphthyl, -(C₁₄)aryl or -(5- to 10-membered)heteroaryl,
 each of which is unsubstituted or substituted with one or more R₆ groups;

25 R₄ is:

(a) $-(C_1-C_{10})$ alkyl, $-(C_2-C_{10})$ alkenyl, $-(C_2-C_{10})$ alkynyl, $-(C_3-C_{10})$ cycloalkyl, $-(C_8-C_{14})$ bicycloalkyl, $-(C_8-C_{14})$ tricycloalkyl, $-(C_5-C_{10})$ cycloalkenyl, $-(C_8-C_{14})$ bicycloalkenyl, $-(C_8-C_{14})$ tricycloalkenyl, $-(3- \text{ to } 7\text{-membered})$ heterocycle, or $-(7- \text{ to } 10\text{-membered})$ bicycloheterocycle, each of which is unsubstituted or substituted with one or
5 more R_5 groups; or

(b) -phenyl, -naphthyl, $-(C_{14})$ aryl or $-(5- \text{ to } 10\text{-membered})$ heteroaryl, each of which is unsubstituted or substituted with one or more R_6 groups;

each R_5 is independently -CN, -OH, $-(C_1-C_6)$ alkyl, $-(C_2-C_6)$ alkenyl, -halo, $-N_3$, $-NO_2$, $-N(R_7)_2$, $-CH=NR_7$, $-NR_7OH$, $-OR_7$, $-COR_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-OC(O)OR_7$,
10 $-SR_7$, $-S(O)R_7$, or $-S(O)_2R_7$;

each R_6 is independently $-(C_1-C_6)$ alkyl, $-(C_2-C_6)$ alkenyl, $-(C_2-C_6)$ alkynyl, $-(C_3-C_8)$ cycloalkyl, $-(C_5-C_8)$ cycloalkenyl, -phenyl, $-(3- \text{ to } 5\text{-membered})$ heterocycle, $-C(halo)_3$, $-CH(halo)_2$, $-CH_2(halo)$, -CN, -OH, -halo, $-N_3$, $-NO_2$, $-N(R_7)_2$, $-CH=NR_7$, $-NR_7OH$, $-OR_7$, $-COR_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-OC(O)OR_7$, $-SR_7$, $-S(O)R_7$, or $-S(O)_2R_7$;

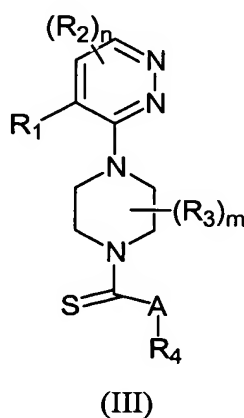
15 each R_7 is independently -H, $-(C_1-C_6)$ alkyl, $-(C_2-C_6)$ alkenyl, $-(C_2-C_6)$ alkynyl, $-(C_3-C_8)$ cycloalkyl, $-(C_5-C_8)$ cycloalkenyl, -phenyl, $-(3- \text{ to } 5\text{-membered})$ heterocycle, $-C(halo)_3$, $-CH(halo)_2$, or $-CH_2(halo)$;

each halo is independently -F, -Cl, -Br, or -I;

n is an integer ranging from 0 to 2; and

20 m is an integer ranging from 0 to 2.

The present invention also encompasses compounds having the formula (III):



and pharmaceutically acceptable salts thereof, wherein:

25 A is -NH- or $-N(C_1-C_6 \text{ alkyl})-$;

R₁ is -halo, -CH₃, -NO₂, -CN, -OH, -OCH₃, -NH₂, C(halo)₃, -CH(halo)₂, or -CH₂(halo);

each R₂ is independently:

(a) -halo, -OH, or -NH₂;

5 (b) -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R₅ groups; or

10 (c) -phenyl, -naphthyl, -(C₁₄)aryl or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R₆ groups;

each R₃ is independently:

(a) -halo, -CN, -OH, -NO₂, or -NH₂;

15 (b) -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R₅ groups; or

20 (c) -phenyl, -naphthyl, -(C₁₄)aryl or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R₆ groups;

R₄ is:

25 (a) -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R₅ groups; or

(b) -phenyl, -naphthyl, -(C₁₄)aryl or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R₆ groups;

30 each R₅ is independently -CN, -OH, -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -halo, -N₃, -NO₂, -N(R₇)₂, -CH=NR₇, -NR₇OH, -OR₇, -COR₇, -C(O)OR₇, -OC(O)R₇, -OC(O)OR₇, -SR₇, -S(O)R₇, or -S(O)₂R₇;

each R_6 is independently $-(C_1-C_6)$ alkyl, $-(C_2-C_6)$ alkenyl, $-(C_2-C_6)$ alkynyl, $-(C_3-C_8)$ cycloalkyl, $-(C_5-C_8)$ cycloalkenyl, -phenyl, -(3- to 5-membered)heterocycle, $-C(halo)_3$, $-CH(halo)_2$, $-CH_2(halo)$, $-CN$, $-OH$, -halo, $-N_3$, $-NO_2$, $-N(R_7)_2$, $-CH=NR_7$, $-NR_7OH$, $-OR_7$, $-COR_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-OC(O)OR_7$, $-SR_7$, $-S(O)R_7$, or $-S(O)_2R_7$;

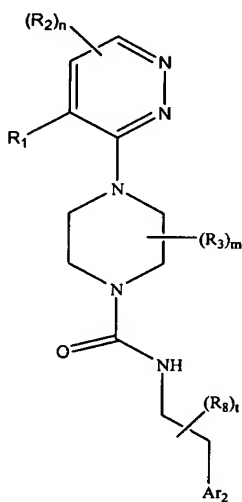
5 each R_7 is independently $-H$, $-(C_1-C_6)$ alkyl, $-(C_2-C_6)$ alkenyl, $-(C_2-C_6)$ alkynyl, $-(C_3-C_8)$ cycloalkyl, $-(C_5-C_8)$ cycloalkenyl, -phenyl, -(3- to 5-membered)heterocycle, $-C(halo)_3$, $-CH(halo)_2$, or $-CH_2(halo)$;

each halo is independently $-F$, $-Cl$, $-Br$, or $-I$;

n is an integer ranging from 0 to 2; and

10 m is an integer ranging from 0 to 2.

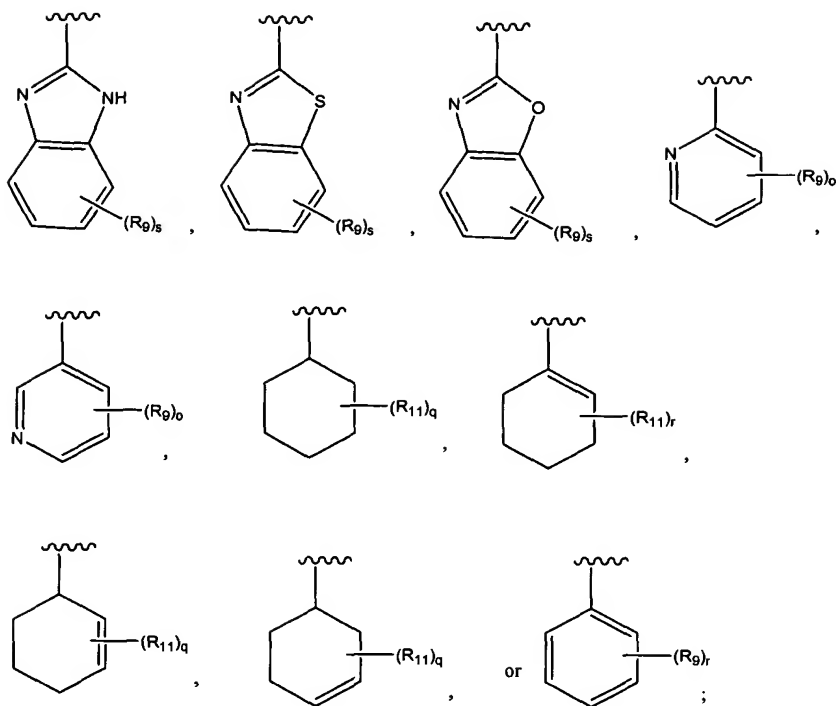
The present invention also encompasses compounds having the formula (IV):



(IV)

15 and pharmaceutically acceptable salts thereof, wherein:

Ar_2 is



R_1 is -H, -halo, -CH₃, -NO₂, -CN, -OH, -OCH₃, -NH₂, C(halo)₃, -CH(halo)₂,

or

-CH₂(halo);

5

each R_2 is independently:

(a) -halo, -CN, -OH, -NO₂, or -NH₂;

(b) -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R_5 groups; or

10

(c) -phenyl, -naphthyl, -(C₁₄)aryl or -(5- to 10-membered)heteroaryl,

each of which is unsubstituted or substituted with one or more R_6 groups;

each R_3 is independently:

15

(a) -halo, -CN, -OH, -NO₂, or -NH₂;

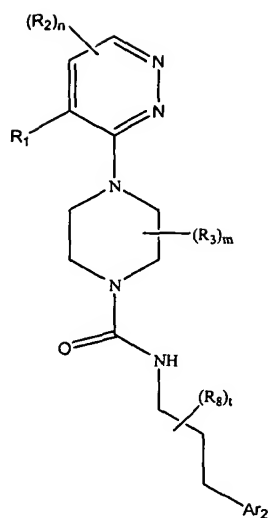
(b) -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R_5 groups; or

20

(c) -phenyl, -naphthyl, -(C₁₄)aryl or -(5- to 10-membered)heteroaryl,

each of which is unsubstituted or substituted with one or more R_6 groups;

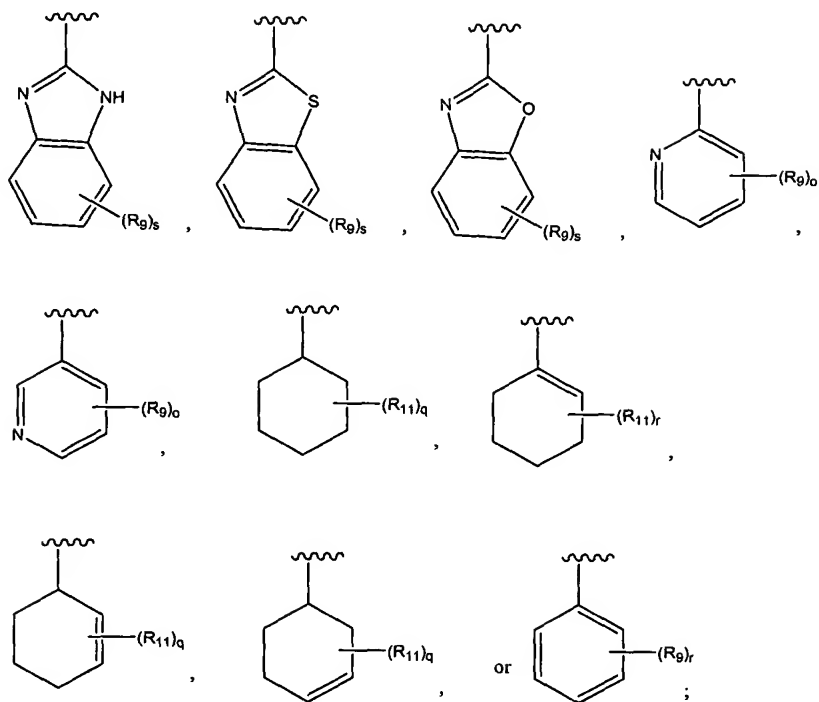
- each R₅ is independently -CN, -OH, -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -halo, -N₃, -NO₂, -N(R₇)₂, -CH=NR₇, -NR₇OH, -OR₇, -COR₇, -C(O)OR₇, -OC(O)R₇, -OC(O)OR₇, -SR₇, -S(O)R₇, or -S(O)₂R₇;
- each R₆ is independently -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -
 5 (C₃-C₈)cycloalkyl, -(C₅-C₈)cycloalkenyl, -phenyl, -(3- to 5-membered)heterocycle, -C(halo)₃, -CH(halo)₂, -CH₂(halo), -CN, -OH, -halo, -N₃, -NO₂, -CH=NR₇, -NR₇OH, -OR₇, -COR₇, -C(O)OR₇, -OC(O)R₇, -OC(O)OR₇, -SR₇, -S(O)R₇, or -S(O)₂R₇;
- each R₇ is independently -H, -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₃-C₈)cycloalkyl, -(C₅-C₈)cycloalkenyl, -phenyl, -(3- to 5-membered)heterocycle,
 10 -C(halo)₃, -CH(halo)₂, or -CH₂(halo);
- each R₈ is independently -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₃-C₈)cycloalkyl, -(C₅-C₈)cycloalkenyl, -phenyl, -(3- to 5-membered)heterocycle, -C(halo)₃, -CH(halo)₂, or CH₂(halo);
- each R₉ is independently -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -
 15 (C₃-C₈)cycloalkyl, -(C₅-C₈)cycloalkenyl, -phenyl, -C(halo)₃, -CH(halo)₂, or CH₂(halo), -CN, -OH, -halo, -N₃, -NO₂, -CH=NR₇, -NR₇OH, -OR₇, -COR₇, -C(O)OR₇, -OC(O)R₇, -OC(O)OR₇, -SR₇, -S(O)R₇, or -S(O)₂R₇;
- each R₁₁ is independently -CN, -OH, -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -halo, -N₃, -NO₂, -N(R₇)₂, -CH=NR₇, -NR₇OH, -OR₇, -COR₇, -C(O)OR₇, -
 20 OC(O)R₇, -OC(O)OR₇, -SR₇, -S(O)R₇, or -S(O)₂R₇;
- each halo is independently -F, -Cl, -Br, or -I;
- n is an integer ranging from 0 to 2;
- m is 0 or 1;
- o is an integer ranging from 0 to 4;
- 25 q is an integer ranging from 0 to 6;
- r is an integer ranging from 0 to 5;
- s is an integer ranging from 0 to 4; and
- t is an integer ranging from 0 to 2.
- The present invention also encompasses compounds having the formula (V):
- 30



(V)

and pharmaceutically acceptable salts thereof, wherein:

Ar₂ is



5

R₁ is -H, -halo, -CH₃, -NO₂, -CN, -OH, -OCH₃, -NH₂, C(halo)₃, -CH(halo)₂,

or

-CH₂(halo);

each R₂ is independently:

10

(a) -halo, -CN, -OH, -NO₂, or -NH₂;

(b) -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-C₁₀)cycloalkenyl, -(C₈-

- C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R₅ groups; or
- (c) -phenyl, -naphthyl, -(C₁₄)aryl or -(5- to 10-membered)heteroaryl,
- 5 each of which is unsubstituted or substituted with one or more R₆ groups;
- each R₃ is independently:
- (a) -halo, -CN, -OH, -NO₂, or -NH₂;
- (b) -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R₅ groups; or
- (c) -phenyl, -naphthyl, -(C₁₄)aryl or -(5- to 10-membered)heteroaryl,
- each of which is unsubstituted or substituted with one or more R₆ groups;
- 15 each R₅ is independently -CN, -OH, -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -halo, -N₃, -NO₂, -N(R₇)₂, -CH=NR₇, -NR₇OH, -OR₇, -COR₇, -C(O)OR₇, -OC(O)R₇, -OC(O)OR₇, -SR₇, -S(O)R₇, or -S(O)₂R₇;
- each R₆ is independently -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₃-C₈)cycloalkyl, -(C₅-C₈)cycloalkenyl, -phenyl, -(3- to 5-membered)heterocycle, -C(halo)₃, -CH(halo)₂, -CH₂(halo), -CN, -OH, -halo, -N₃, -NO₂, -CH=NR₇, -NR₇OH, -OR₇, -COR₇, -C(O)OR₇, -OC(O)R₇, -OC(O)OR₇, -SR₇, -S(O)R₇, or -S(O)₂R₇;
- 20 each R₇ is independently -H, -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₃-C₈)cycloalkyl, -(C₅-C₈)cycloalkenyl, -phenyl, -(3- to 5-membered)heterocycle, -C(halo)₃, -CH(halo)₂, or -CH₂(halo);
- 25 each R₈ is independently -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₃-C₈)cycloalkyl, -(C₅-C₈)cycloalkenyl, -phenyl, -(3- to 5-membered)heterocycle, -C(halo)₃, -CH(halo)₂, or CH₂(halo);
- each R₉ is independently -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₃-C₈)cycloalkyl, -(C₅-C₈)cycloalkenyl, -phenyl, -C(halo)₃, -CH(halo)₂, or CH₂(halo), -CN, -OH, -halo, -N₃, -NO₂, -CH=NR₇, -NR₇OH, -OR₇, -COR₇, -C(O)OR₇, -OC(O)R₇, -OC(O)OR₇, -SR₇, -S(O)R₇, or -S(O)₂R₇;
- 30 each R₁₁ is independently -CN, -OH, -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -halo, -N₃, -NO₂, -N(R₇)₂, -CH=NR₇, -NR₇OH, -OR₇, -COR₇, -C(O)OR₇, -OC(O)R₇, -OC(O)OR₇, -SR₇, -S(O)R₇, or -S(O)₂R₇;
- 35

each halo is independently -F, -Cl, -Br, or -I;

n is an integer ranging from 0 to 2;

m is 0 or 1;

o is an integer ranging from 0 to 4;

5 q is an integer ranging from 0 to 6;

r is an integer ranging from 0 to 5;

s is an integer ranging from 0 to 4; and

t is an integer ranging from 0 to 2.

A compound of formula (I), (II), (III), (IV), or (V) or a pharmaceutically
10 acceptable salt thereof (a “Pyridazinylpiperazine Compound”) is useful for treating or
preventing pain, UI, an ulcer, IBD, IBS, an addictive disorder, Parkinson’s disease,
parkinsonism, anxiety, epilepsy, stroke, a seizure, a pruritic condition, psychosis, a
cognitive disorder, a memory deficit, restricted brain function, Huntington’s chorea, ALS,
dementia, retinopathy, a muscle spasm, a migraine, vomiting, dyskinesia, or depression
15 (each being a “Condition”) in an animal.

The invention also relates to compositions comprising an effective amount of
a Pyridazinylpiperazine Compound and a pharmaceutically acceptable carrier or excipient.
The compositions are useful for treating or preventing a Condition in an animal.

The invention further relates to methods for treating a Condition, comprising
20 administering to an animal in need thereof an effective amount of a Pyridazinylpiperazine
Compound.

The invention further relates to methods for preventing a Condition,
comprising administering to an animal in need thereof an effective amount of a
Pyridazinylpiperazine Compound.

25 The invention still further relates to methods for inhibiting Vanilloid
Receptor 1 (“VR1”) function in a cell, comprising contacting a cell capable of expressing
VR1 with an effective amount of a Pyridazinylpiperazine Compound.

The invention still further relates to methods for inhibiting mGluR5 function
in a cell, comprising contacting a cell capable of expressing mGluR5 with an effective
30 amount of a Pyridazinylpiperazine Compound.

The invention still further relates to methods for inhibiting metabotropic
glutamate receptor 1 (“mGluR1”) function in a cell, comprising contacting a cell capable of
expressing mGluR1 with an effective amount of a Pyridazinylpiperazine Compound.

The invention still further relates to methods for preparing a composition, comprising the step of admixing a Pyridazinylpiperazine Compound and a pharmaceutically acceptable carrier or excipient.

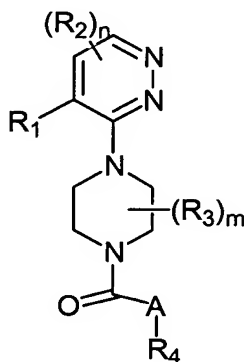
5 The invention still further relates to a kit comprising a container containing an effective amount of a Pyridazinylpiperazine Compound.

The present invention can be understood more fully by reference to the following detailed description and illustrative examples, which are intended to exemplify non-limiting embodiments of the invention.

10 3. DETAILED DESCRIPTION OF THE INVENTION

3.1. PYRIDAZINYLPIPERAZINE COMPOUNDS OF FORMULA (I)

As stated above, the present invention encompasses compounds of Formula (I):



15 (I)

and pharmaceutically acceptable salts thereof, where A, R₁-R₄, n and m are defined above for the Pyridazinylpiperazine Compounds of formula (I).

In one embodiment, A is -NH-.

In another embodiment, A is -N(C₁-C₆)alkyl-.

20 In another embodiment, A is -N-(O-C₁-C₆ alkyl)-.

In another embodiment, R₁ is -halo, -CH₃, -NO₂, -CN, -OH, -OCH₃, C(halo)₃, -CH(halo)₂, or -CH₂(halo);

In another embodiment, R₁ is -halo.

In another embodiment, R₁ is -Cl.

25 In another embodiment, R₁ is -Br.

In another embodiment, R₁ is -I.

In another embodiment, R₁ is -F.

In another embodiment, R₁ is -CH₃.

In another embodiment, R₁ is -NO₂.

5 In another embodiment, R₁ is -CN.

In another embodiment, R₁ is -OH.

In another embodiment, R₁ is -OCH₃.

In another embodiment, R₁ is -NH₂.

In another embodiment, R₁ is -C(halo)₃.

10 In another embodiment, R₁ is -CH(halo)₂.

In another embodiment, R₁ is -CH₂(halo).

In another embodiment, R₂ is -halo, -OH, or -NH₂.

In another embodiment, n is 1 and R₂ is -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(3- to 7-

15 membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R₅ groups.

In another embodiment, n is 1 and R₂ is -phenyl, -naphthyl, -(C₁₄)aryl or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more

20 R₆ groups.

In another embodiment, m is 1 and R₃ is -halo, -CN, -OH, -NO₂, or -NH₂.

In another embodiment, m is 1 and R₃ is -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(3- to 7-

25 membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R₅ groups.

In another embodiment, m is 1 and R₃ is -phenyl, -naphthyl, -(C₁₄)aryl or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more

R₆ groups.

30 In another embodiment, m is 1 and R₃ is -CH₃.

In another embodiment, m is 1, R_3 is $-CH_3$, and the carbon atom to which the R_3 is attached is in the (R)-configuration.

In another embodiment, m is 1, R_3 is $-CH_3$, and the carbon atom to which the R_3 is attached is in the (S)-configuration.

5 In another embodiment, R_4 is $-(C_1-C_{10})$ alkyl, $-(C_2-C_{10})$ alkenyl, $-(C_2-C_{10})$ alkynyl, $-(C_3-C_{10})$ cycloalkyl, $-(C_8-C_{14})$ bicycloalkyl, $-(C_8-C_{14})$ tricycloalkyl, $-(C_5-C_{10})$ cycloalkenyl, $-(C_8-C_{14})$ bicycloalkenyl, $-(C_8-C_{14})$ tricycloalkenyl, $-(3- \text{ to } 7-$ membered)heterocycle, or $-(7- \text{ to } 10-$ membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R_5 groups. In another embodiment, the R_4 group is unsubstituted. In another embodiment, the R_4 group is substituted with one R_5 group.

In another embodiment, R_4 is $-\text{phenyl}$, $-\text{naphthyl}$, $-(C_{14})$ aryl or $-(5- \text{ to } 10-$ membered)heteroaryl, each of which is unsubstituted or substituted with one or more R_6 groups.

15 In another embodiment R_4 is $-\text{phenyl}$, $-\text{naphthyl}$, $-(C_{14})$ aryl or $-(5- \text{ to } 10-$ membered)heteroaryl, each of which is unsubstituted or substituted with one or more R_6 groups. In another embodiment the R_4 is unsubstituted. In another embodiment R_4 is substituted with one R_6 group. In another embodiment R_6 is a $-C_1-C_6$ alkyl. In another embodiment R_4 is an unsubstituted phenyl. In another embodiment R_4 is $-\text{phenyl}$ substituted with an R_6 group. In another embodiment the R_6 group is substituted at the 4-position of the $-\text{phenyl}$.

In another embodiment, R_4 is phenyl.

25 In another embodiment, n and m are 0 and R_4 is $-\text{phenyl}$. In another embodiment, the $-\text{phenyl}$ is substituted with a $-(C_1-C_6)$ alkyl group. In another embodiment, the $-(C_1-C_6)$ alkyl group is substituted at the 4-position of the $-\text{phenyl}$. In another embodiment, the $-(C_1-C_6)$ alkyl group is a *t*-butyl group substituted at the 4-position of the $-\text{phenyl}$. In another embodiment, the $-(C_1-C_6)$ alkyl group is an *iso*-propyl group substituted at the 4-position of the $-\text{phenyl}$.

30 In another embodiment, n and m are 0, R_1 is methyl, and R_4 is $-\text{phenyl}$. In another embodiment, the $-\text{phenyl}$ is substituted with a $-(C_1-C_6)$ alkyl group. In another embodiment, the $-(C_1-C_6)$ alkyl group is substituted at the 4-position of the $-\text{phenyl}$. In another embodiment, the $-(C_1-C_6)$ alkyl group is a *t*-butyl group or an *iso*-propyl group substituted at the 4-position of the $-\text{phenyl}$.

In another embodiment, n and m are 0 and R₄ is -phenyl substituted at its 4-position with a -CF₃ group.

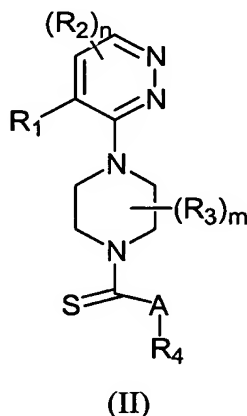
In another embodiment, n and m are 0 and R₄ is -phenyl substituted at its 4-position with a -OCF₃ group.

5 In another embodiment, n is 0, m is 1, R₃ is methyl, and R₄ is -phenyl substituted at its 4-position with a -CF₃ group.

In another embodiment, n is 0, m is 1, R₃ is methyl, and R₄ is -phenyl substituted at its 4-position with a -OCF₃ group.

3.2. PYRIDAZINYLPYPERAZINE COMPOUNDS OF FORMULA (II)

10 The present invention also encompasses compounds of formula (II):



and pharmaceutically acceptable salts thereof, where A, R₁-R₄, n and m are defined above for the Pyridazinyllpiperazine Compounds of formula (II).

15 In one embodiment, A is -N(O-C₁-C₆ alkyl)-.

In another embodiment, A is -CH₂-.

In another embodiment, A is -CH₂CH₂-.

In another embodiment, A is -CH=CH-.

In another embodiment A is -CH=CH- in the *trans* configuration.

20 In another embodiment A is -CH=CH- in the *cis* configuration.

In another embodiment, R₁ is -halo, -CH₃, -NO₂, -CN, -OH, -OCH₃, C(halo)₃, -CH(halo)₂, or -CH₂(halo);

In another embodiment, R₁ is -halo.

In another embodiment, R₁ is -Cl.

In another embodiment, R₁ is -Br.

In another embodiment, R₁ is -I.

In another embodiment, R₁ is -F.

In another embodiment, R₁ is -CH₃.

5 In another embodiment, R₁ is -NO₂.

In another embodiment, R₁ is -CN.

In another embodiment, R₁ is -OH.

In another embodiment, R₁ is -OCH₃.

In another embodiment, R₁ is -NH₂.

10 In another embodiment, R₁ is -C(halo)₃.

In another embodiment, R₁ is -CH(halo)₂.

In another embodiment, R₁ is -CH₂(halo).

In another embodiment, n is 1 and R₂ is -halo, -CN, -OH, -NO₂, or -NH₂.

15 In another embodiment, n is 1 and R₂ is -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R₅ groups.

20 In another embodiment, n is 1 and R₂ is -phenyl, -naphthyl, -(C₁₄)aryl or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R₆ groups.

In another embodiment, m is 1 and R₃ is -halo, -CN, -OH, -NO₂, or -NH₂.

25 In another embodiment, R₃ is -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R₅ groups.

30 In another embodiment, m is 1 and R₃ is -phenyl, -naphthyl, -(C₁₄)aryl or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R₆ groups.

In another embodiment, m is 1 and R₃ is -CH₃.

In another embodiment, m is 1, R₃ is -CH₃, and the carbon atom to which the R₃ is attached is in the (R)-configuration.

5 In another embodiment, m is 1, R₃ is -CH₃, and the carbon atom to which the R₃ is attached is in the (S)-configuration.

In another embodiment R₄ is -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is
10 unsubstituted or substituted with one or more R₅ groups. In another embodiment the R₄ is unsubstituted. In another embodiment the R₄ is substituted with one R₅ group.

In another embodiment R₄ is -phenyl, -naphthyl, -(C₁₄)aryl or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R₆ groups. In another embodiment the R₄ is unsubstituted. In another embodiment R₄ is
15 substituted with one R₆ group. In another embodiment R₆ is a -C₁-C₆ alkyl. In another embodiment R₄ is an unsubstituted phenyl. In another embodiment R₄ is -phenyl substituted with an R₆ group. In another embodiment the R₆ group is substituted at the 4-position of the -phenyl.

In another embodiment, R₄ is phenyl.

20 In another embodiment, n and m are 0 and R₄ is -phenyl. In another embodiment, the -phenyl is substituted with a -(C₁-C₆) alkyl group. In another embodiment, the -(C₁-C₆) alkyl group is substituted at the 4-position of the -phenyl. In another embodiment, the -(C₁-C₆) alkyl group is a *t*-butyl group substituted at 4-position of the -phenyl. In another embodiment, the -(C₁-C₆) alkyl group is an *iso*-propyl group substituted
25 at the 4-position of the -phenyl.

In another embodiment, n and m are 0, R₁ is methyl, and R₄ is -phenyl. In another embodiment, the -phenyl is substituted with a -(C₁-C₆) alkyl group. In another embodiment, the -(C₁-C₆) alkyl group is substituted at the 4-position of the -phenyl. In another embodiment, the -(C₁-C₆) alkyl group is a *t*-butyl group or an *iso*-propyl group
30 substituted at the 4-position of the -phenyl.

In another embodiment, n and m are 0 and R₄ is -phenyl substituted at its 4-position with a -CF₃ group.

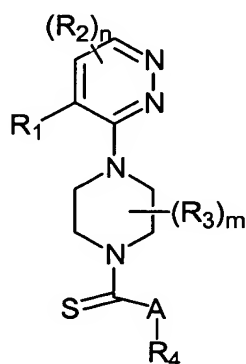
In another embodiment, n and m are 0 and R₄ is -phenyl substituted at its 4-position with a -OCF₃ group.

In another embodiment, n is 0, m is 1, R₃ is methyl, and R₄ is -phenyl substituted at its 4-position with a -CF₃ group.

5 In another embodiment, n is 0, m is 1, R₃ is methyl, and R₄ is -phenyl substituted at its 4-position with a -OCF₃ group.

3.3. PYRIDAZINYLPYPERAZINE COMPOUNDS OF FORMULA (III)

The present invention also encompasses compounds of formula (III):



10

(III)

and pharmaceutically acceptable salts thereof, where A, R₁-R₄, n and m are defined above for the Pyridazinyloperazine Compounds of formula (III).

In one embodiment A is -NH-.

In another embodiment, A is -N(C₁-C₆ alkyl)-.

15

In another embodiment, R₁ is -halo, -CH₃, -NO₂, -CN, -OH, -OCH₃, C(halo)₃, -CH(halo)₂, or -CH₂(halo);

In another embodiment, R₁ is -halo.

In another embodiment, R₁ is -Cl.

In another embodiment, R₁ is -Br.

20

In another embodiment, R₁ is -I.

In another embodiment, R₁ is -F.

In another embodiment, R₁ is -CH₃.

In another embodiment, R₁ is -NO₂.

In another embodiment, R₁ is -CN

In another embodiment, R₁ is -OH.

In another embodiment, R₁ is -OCH₃.

In another embodiment, R₁ is -NH₂.

In another embodiment, R₁ is -C(halo)₃.

5 In another embodiment, R₁ is -CH(halo)₂.

In another embodiment, R₁ is -CH₂(halo).

In another embodiment, n is 1 and R₂ is -halo, -OH, or -NH₂.

In another embodiment, n is 1 and R₂ is -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R₅ groups.

15 In another embodiment, n is 1 and R₂ is -phenyl, -naphthyl, -(C₁₄)aryl or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R₆ groups.

In another embodiment, m is 1 and R₃ is -halo, -CN, -OH, -NO₂, or -NH₂.

20 In another embodiment, m is 1 and R₃ is -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R₅ groups.

In another embodiment, m is 1 and R₃ is -phenyl, -naphthyl, -(C₁₄)aryl or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R₆ groups.

25 In another embodiment, m is 1 and R₃ is -CH₃.

In another embodiment, m is 1, R₃ is -CH₃, and the carbon atom to which the R₃ is attached is in the (R)-configuration.

In another embodiment, m is 1, R₃ is -CH₃, and the carbon atom to which the R₃ is attached is in the (S)-configuration.

30 In another embodiment R₄ is -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-

C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R₅ groups. In another embodiment the R₄ is unsubstituted. In another embodiment the R₄ is substituted with one R₅ group.

5 In another embodiment R₄ is -phenyl, -naphthyl, -(C₁₄)aryl or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R₆ groups. In another embodiment the R₄ is unsubstituted. In another embodiment R₄ is substituted with one R₆ group. In another embodiment R₆ is a -C₁-C₆ alkyl. In another embodiment R₄ is an unsubstituted phenyl. In another embodiment R₄ is -phenyl
10 substituted with an R₆ group. In another embodiment the R₆ group is substituted at the 4-position of the -phenyl.

 In another embodiment, R₄ is phenyl.

 In another embodiment, n and m are 0 and R₄ is -phenyl. In another embodiment, the -phenyl is substituted with a -(C₁-C₆) alkyl group. In another embodiment,
15 the -(C₁-C₆) alkyl group is substituted at the 4-position of the -phenyl. In another embodiment, the -(C₁-C₆) alkyl group is a *t*-butyl group substituted at 4-position of the -phenyl. In another embodiment, the -(C₁-C₆) alkyl group is an *iso*-propyl group substituted at the 4-position of the -phenyl.

 In another embodiment, n and m are 0, R₁ is methyl, and R₄ is -phenyl. In
20 another embodiment, the -phenyl is substituted with a -(C₁-C₆) alkyl group. In another embodiment, the -(C₁-C₆) alkyl group is substituted at the 4-position of the -phenyl. In another embodiment, the -(C₁-C₆) alkyl group is a *t*-butyl group or an *iso*-propyl group substituted at the 4-position of the -phenyl.

 In another embodiment, n and m are 0 and R₄ is -phenyl substituted at its 4-
25 position with a -CF₃ group.

 In another embodiment, n and m are 0 and R₄ is -phenyl substituted at its 4-position with a -OCF₃ group.

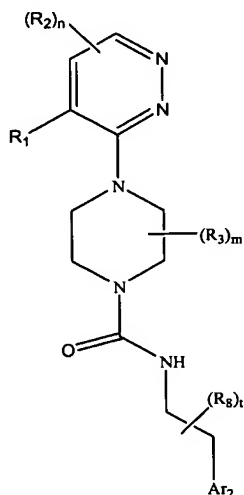
 In another embodiment, n is 0, m is 1, R₃ is methyl, and R₄ is -phenyl substituted at its 4-position with a -CF₃ group.

30 In another embodiment, n is 0, m is 1, R₃ is methyl, and R₄ is -phenyl substituted at its 4-position with a -OCF₃ group.

 In another embodiment n is 1 and R₂ is -halo, -OH, or -NH₂.

3.4. PYRIDAZINYLPIPERAZINE COMPOUNDS OF FORMULA (IV)

The present invention also encompasses compounds of formula (IV):



(IV)

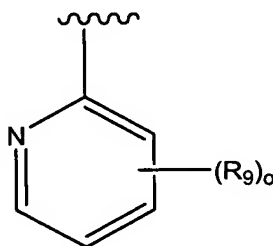
and pharmaceutically acceptable salts thereof, where Ar_2 , R_1 , R_2 , R_3 , R_8 , n , m , and t are defined above for the Pyridazinylpiperazine Compounds of formula (IV).

In one embodiment, Ar_2 is a benzothiazolyl group.

In another embodiment, Ar_2 is a benzoimidazolyl group.

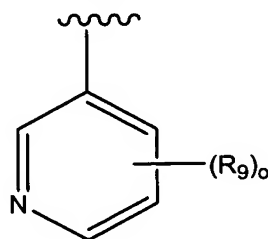
In another embodiment, Ar_2 is a benzooxazolyl group.

In another embodiment, Ar_2 is



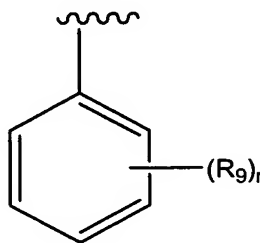
wherein R_9 and o are defined above for the Pyridazinylpiperazine Compounds of formula (IV).

In another embodiment, Ar_2 is



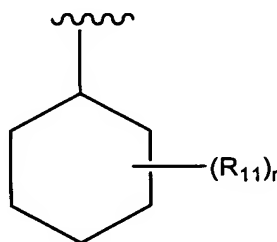
wherein R_9 and o are defined above for the Pyridazinylpiperazine Compounds of formula (IV).

In another embodiment, Ar_2 is



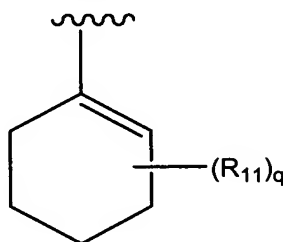
- 5 wherein R_9 and r are defined above for the Pyridazinylpiperazine Compounds of formula (IV).

In another embodiment, Ar_2 is



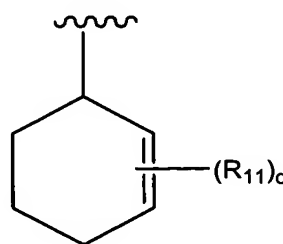
- 10 wherein R_{11} and r are defined above for the Pyridazinylpiperazine Compounds of formula (IV).

In another embodiment, Ar_2 is



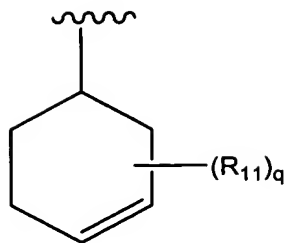
- 15 wherein R_{11} and q are defined above for the Pyridazinylpiperazine Compounds of formula (IV).

In another embodiment, Ar_2 is



wherein R_{11} and q are defined above for the Pyridazinylpiperazine Compounds of formula (IV).

In another embodiment, Ar_2 is



wherein R_{11} and q are defined above for the Pyridazinylpiperazine Compounds of formula (IV).

- In another embodiment, R_1 is -H.
- 5 In another embodiment, R_1 is -halo.
- In another embodiment, R_1 is -Cl.
- In another embodiment, R_1 is -Br.
- In another embodiment, R_1 is -I.
- In another embodiment, R_1 is -F.
- 10 In another embodiment, R_1 is -CH₃.
- In another embodiment, R_1 is -NO₂.
- In another embodiment, R_1 is -CN.
- In another embodiment, R_1 is -OH.
- In another embodiment, R_1 is -OCH₃.
- 15 In another embodiment, R_1 is -NH₂.
- In another embodiment, R_1 is -C(halo)₃.
- In another embodiment, R_1 is -CH(halo)₂.
- In another embodiment, R_1 is -CH₂(halo).
- In another embodiment, n is 1 and R_2 is -halo, -OH, or -NH₂.
- 20 In another embodiment, n is 1 and R_2 is -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R_5 groups.
- 25 In another embodiment, n is 1 and R_2 is -phenyl, -naphthyl, -(C₁₄)aryl or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R_6 groups.
- In another embodiment, m is 1 and R_3 is -halo, -CN, -OH, -NO₂, or -NH₂.
- In another embodiment, m is 1 and R_3 is -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(3- to 7-
- 30

membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R₅ groups.

In another embodiment, m is 1 and R₃ is -phenyl, -naphthyl, -(C₁₄)aryl or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R₆ groups.

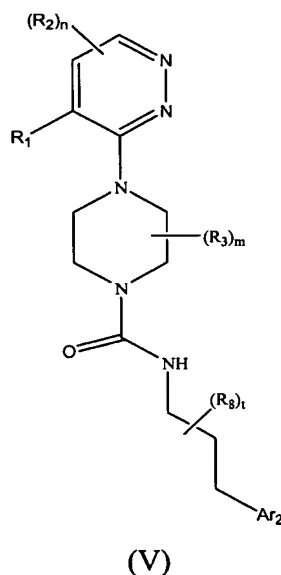
In another embodiment, m is 1 and R₃ is -CH₃.

In another embodiment, m is 1, R₃ is -CH₃, and the carbon atom to which the R₃ is attached is in the (R)-configuration.

In another embodiment, m is 1, R₃ is -CH₃, and the carbon atom to which the R₃ is attached is in the (S)-configuration.

3.5. PYRIDAZINYLPIPERAZINE COMPOUNDS OF FORMULA (V)

The present invention also encompasses compounds of formula (V):



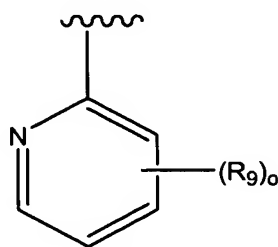
and pharmaceutically acceptable salts thereof, where Ar₂, R₁, R₂, R₃, R₈, n, m, and t are defined above for the Pyridazinylpiperazine Compounds of formula (V).

In one embodiment, Ar₂ is a benzothiazolyl group.

In another embodiment, Ar₂ is a benzoimidazolyl group.

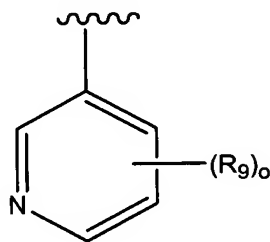
In another embodiment, Ar₂ is a benzooxazolyl group.

In another embodiment, Ar₂ is



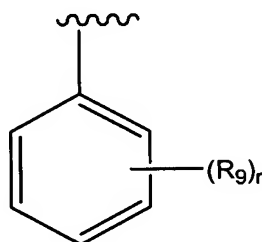
wherein R_9 and o are defined above for the Pyridazinylpiperazine Compounds of formula (V).

In another embodiment, Ar_2 is



5 wherein R_9 and o are defined above for the Pyridazinylpiperazine Compounds of formula (V).

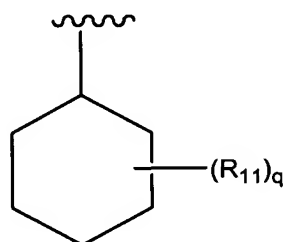
In another embodiment, Ar_2 is



wherein R_9 and r are defined above for the Pyridazinylpiperazine Compounds of formula

10 (V).

In another embodiment, Ar_2 is

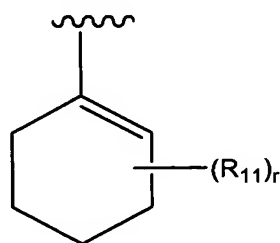


wherein R_{11} and q are defined above for the Pyridazinylpiperazine Compounds of formula

(V).

15

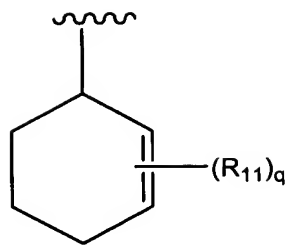
In another embodiment, Ar_2 is



wherein R_{11} and r are defined above for the Pyridazinylpiperazine Compounds of formula

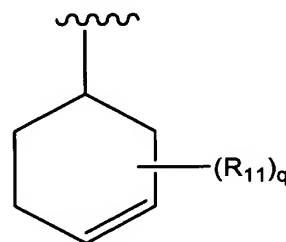
(V).

In another embodiment, Ar_2 is



wherein R_{11} and q are defined above for the Pyridazinylpiperazine Compounds of formula (V).

In another embodiment, Ar_2 is



5

wherein R_{11} and q are defined above for the Pyridazinylpiperazine Compounds of formula (V).

In another embodiment, R_1 is -H.

In another embodiment, R_1 is -halo.

10

In another embodiment, R_1 is -Cl.

In another embodiment, R_1 is -Br.

In another embodiment, R_1 is -I.

In another embodiment, R_1 is -F.

In another embodiment, R_1 is -CH₃.

15

In another embodiment, R_1 is -NO₂.

In another embodiment, R_1 is -CN.

In another embodiment, R_1 is -OH.

In another embodiment, R_1 is -OCH₃.

In another embodiment, R_1 is -NH₂.

20

In another embodiment, R_1 is -C(halo)₃.

In another embodiment, R_1 is -CH(halo)₂.

In another embodiment, R_1 is -CH₂(halo).

In another embodiment, n is 1 and R_2 is -halo, -OH, or -NH₂.

25 In another embodiment, n is 1 and R_2 is -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(3- to 7-

membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R₅ groups.

5 In another embodiment, n is 1 and R₂ is -phenyl, -naphthyl, -(C₁₄)aryl or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R₆ groups.

In another embodiment, m is 1 and R₃ is -halo, -CN, -OH, -NO₂, or -NH₂.

10 In another embodiment, m is 1 and R₃ is -(C₁-C₁₀)alkyl, -(C₂-C₁₀)alkenyl, -(C₂-C₁₀)alkynyl, -(C₃-C₁₀)cycloalkyl, -(C₈-C₁₄)bicycloalkyl, -(C₈-C₁₄)tricycloalkyl, -(C₅-C₁₀)cycloalkenyl, -(C₈-C₁₄)bicycloalkenyl, -(C₈-C₁₄)tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R₅ groups.

In another embodiment, m is 1 and R₃ is -phenyl, -naphthyl, -(C₁₄)aryl or -(5- to 10-membered)heteroaryl, each of which is unsubstituted or substituted with one or more R₆ groups.

15 In another embodiment, m is 1 and R₃ is -CH₃.

In another embodiment, m is 1, R₃ is -CH₃, and the carbon atom to which the R₃ is attached is in the (R)-configuration.

In another embodiment, m is 1, R₃ is -CH₃, and the carbon atom to which the R₃ is attached is in the (S)-configuration.

20 **3.6. PYRIDAZINYLPYPERAZINE COMPOUNDS OF FORMULAS (I) TO (V)**

Certain Pyridazinylpiperazine Compounds may have asymmetric centers and therefore exist in different enantiomeric and diastereomeric forms. A Pyridazinylpiperazine Compound can be in the form of an optical isomer or a diastereomer. Accordingly, the invention encompasses Pyridazinylpiperazine Compounds and their uses as described herein in the form of their optical isomers, diastereomers, and mixtures thereof, including a racemic mixture.

30 In the Pyridazinylpiperazine Compounds each R₃ can be on any carbon of the piperazine ring. In one embodiment, the Pyridazinylpiperazine Compounds have only one R₃ group, and that R₃ group is attached to a carbon atom adjacent to the nitrogen atom attached to the pyridazinyl group. In another embodiment, the Pyridazinylpiperazine Compound has only one R₃ group, and that R₃ group is attached to a carbon atom adjacent to the nitrogen atom attached to the -C(=O)-A-R₄, -C(=S)-A-R₄, phenethyl, or phenpropyl group.

In another embodiment, two R₃ groups are on a single atom of the piperazine ring. In another embodiment, an R₃ group is attached to a carbon atom adjacent to the nitrogen atom attached to the pyridazinyl group and another R₃ group is attached to a carbon atom adjacent to the nitrogen atom attached to the -C(=O)-A-R₄, -C(=S)-A-R₄, phenethyl, or phenpropyl group.

In another embodiment, the Pyridazinylpiperazine Compound has two R₃ groups, each being attached to a different carbon atom adjacent to a nitrogen atom attached to the pyridazinyl group. In another embodiment, the Pyridazinylpiperazine Compound has two R₃ groups, each being attached to a different carbon atom adjacent to a nitrogen atom attached to the -C(=O)-A-R₄, -C(=S)-A-R₄, phenethyl, or phenpropyl group.

In one embodiment, wherein the Pyridazinylpiperazine Compound has one or two R₃ groups, the carbon atom to which an R₃ group is attached has the (R) configuration. In another embodiment, wherein the Pyridazinylpiperazine Compound has one or two R₃ groups, the carbon atom to which the R₃ group is attached has the (S) configuration. In another embodiment, the Pyridazinylpiperazine Compound has one or two R₃ groups, and at least one of the carbon atoms to which an R₃ group is attached has the (R) configuration. In another embodiment, the Pyridazinylpiperazine Compound has one or two R₃ groups, and at least one of the carbon atoms to which an R₃ group is attached has the (S) configuration.

In another embodiment, the Pyridazinylpiperazine Compound has one or two R₃ groups, and an R₃ group is attached to a carbon atom adjacent to a nitrogen atom attached to the pyridazinyl group, and the carbon to which the R₃ group is attached is in the (R) configuration. In another embodiment, the Pyridazinylpiperazine Compound has one or two R₃ groups, an R₃ group is attached to a carbon atom adjacent to a nitrogen attached to the pyridazinyl group, the carbon to which the R₃ group is attached is in the (R) configuration, and R₃ is -(C₁-C₄)alkyl unsubstituted or substituted with one or more halo groups. In another embodiment, the Pyridazinylpiperazine Compound has one or two R₃ groups, an R₃ group is attached to a carbon atom adjacent to a nitrogen attached to the pyridazinyl group, the carbon to which the R₃ group is attached is in the (R) configuration, and R₃ is -CH₃. In another embodiment, the Pyridazinylpiperazine Compound has one or two R₃ groups, an R₃ group is attached to a carbon atom adjacent to a nitrogen attached to the pyridazinyl group, the carbon to which the R₃ group is attached is in the (R) configuration, and R₃ is -CF₃. In another embodiment, the Pyridazinylpiperazine Compound has one or two R₃ groups, an R₃ group is attached to a carbon atom adjacent to a nitrogen

attached to the pyridazinyl group, the carbon to which the R₃ group is attached is in the (R) configuration, and R₃ is -CH₂CH₃.

In another embodiment, the Pyridazinylpiperazine Compound has one or two R₃ groups, an R₃ group is attached to a carbon atom adjacent to a nitrogen atom attached to the -C(=O)-A-R₄, -C(=S)-A-R₄, phenethyl, or phenpropyl group, and the carbon to which the R₃ group is attached is in the (R) configuration. In another embodiment, the Pyridazinylpiperazine Compound has one or two R₃ groups, an R₃ group is attached to a carbon atom adjacent to a nitrogen attached to the -C(=O)-A-R₄, -C(=S)-A-R₄, phenethyl, or phenpropyl group, the carbon to which the R₃ group is attached is in the (R) configuration, and R₃ is -(C₁-C₄)alkyl unsubstituted or substituted with one or more halo groups. In another embodiment, the Pyridazinylpiperazine Compound has one or two R₃ groups, an R₃ group is attached to a carbon atom adjacent to a nitrogen attached to the -C(=O)-A-R₄, -C(=S)-A-R₄, phenethyl, or phenpropyl group, the carbon to which the R₃ group is attached is in the (R) configuration, and R₃ is -CH₃. In another embodiment, the Pyridazinylpiperazine Compound has one or two R₃ groups, an R₃ group is attached to a carbon atom adjacent to a nitrogen attached to the -C(=O)-A-R₄, -C(=S)-A-R₄, phenethyl, or phenpropyl group, the carbon to which the R₃ group is attached is in the (R) configuration, and R₃ is -CF₃. In another embodiment, the Pyridazinylpiperazine Compound has one or two R₃ groups, an R₃ group is attached to a carbon atom adjacent to a nitrogen attached to the -C(=O)-A-R₄, -C(=S)-A-R₄, phenethyl, or phenpropyl group, the carbon to which the R₃ group is attached is in the (R) configuration, and R₃ is -CH₂CH₃.

In another embodiment, the Pyridazinylpiperazine Compound has one or two R₃ groups, an R₃ group is attached to a carbon atom adjacent to a nitrogen atom attached to the pyridazinyl group, and the carbon to which the R₃ group is attached is in the (S) configuration. In another embodiment, the Pyridazinylpiperazine Compound has one or two R₃ groups, an R₃ group is attached to a carbon atom adjacent to a nitrogen attached to the pyridazinyl group, the carbon to which the R₃ group is attached is in the (S) configuration, and R₃ is -(C₁-C₄)alkyl unsubstituted or substituted with one or more halo groups. In another embodiment, the Pyridazinylpiperazine Compound has one or two R₃ groups, an R₃ group is attached to a carbon atom adjacent to a nitrogen attached to the pyridazinyl group, the carbon to which the R₃ group is attached is in the (S) configuration, and R₃ is -CH₃. In another embodiment, the Pyridazinylpiperazine Compound has one or two R₃ groups, an R₃ group is attached to a carbon atom adjacent to a nitrogen attached to the pyridazinyl group, the carbon to which the R₃ group is attached is in the (S) configuration, and R₃ is -CF₃. In another embodiment, the Pyridazinylpiperazine Compound has one or two R₃ groups, an R₃

group is attached to a carbon atom adjacent to a nitrogen attached to the pyridazinyl group, the carbon to which the R₃ group is attached is in the (S) configuration, and R₃ is -CH₂CH₃.

In another embodiment, the Pyridazinylpiperazine Compound has one or two R₃ groups, an R₃ group is attached to a carbon atom adjacent to a nitrogen atom attached to the -C(=O)-A-R₄, -C(=S)-A-R₄, phenethyl, or phenpropyl group, and the carbon to which the R₃ group is attached is in the (S) configuration. In another embodiment, the Pyridazinylpiperazine Compound has one or two R₃ groups, an R₃ group is attached to a carbon atom adjacent to a nitrogen attached to the -C(=O)-A-R₄, -C(=S)-A-R₄, phenethyl, or phenpropyl group, the carbon to which the R₃ group is attached is in the (S) configuration, and R₃ is -(C₁-C₄)alkyl unsubstituted or substituted with one or more halo groups. In another embodiment, the Pyridazinylpiperazine Compound has one or two R₃ groups, an R₃ group is attached to a carbon atom adjacent to a nitrogen attached to the -C(=O)-A-R₄, -C(=S)-A-R₄, phenethyl, or phenpropyl group, the carbon to which the R₃ group is attached is in the (S) configuration, and R₃ is -CH₃. In another embodiment, the Pyridazinylpiperazine Compound has one or two R₃ groups, an R₃ group is attached to a carbon atom adjacent to a nitrogen attached to the -C(=O)-A-R₄, -C(=S)-A-R₄, phenethyl, or phenpropyl group, the carbon to which the R₃ group is attached is in the (S) configuration, and R₃ is -CF₃. In another embodiment, the Pyridazinylpiperazine Compound has one or two R₃ groups, an R₃ group is attached to a carbon atom adjacent to a nitrogen attached to the -C(=O)-A-R₄, -C(=S)-A-R₄, phenethyl, or phenpropyl group, the carbon to which the R₃ group is attached is in the (S) configuration, and R₃ is -CH₂CH₃.

In another embodiment, the Pyridazinylpiperazine Compound has only one R₃ group, the R₃ group is attached to a carbon atom adjacent to a nitrogen atom attached to the pyridazinyl group, and the carbon to which the R₃ group is attached is in the (R) configuration. In another embodiment, the Pyridazinylpiperazine Compound has only one R₃ group, the R₃ group is attached to a carbon atom adjacent to a nitrogen attached to the pyridazinyl group, the carbon to which the R₃ group is attached is in the (R) configuration, and R₃ is -(C₁-C₄)alkyl unsubstituted or substituted with one or more halo groups. In another embodiment, the Pyridazinylpiperazine Compound has only one R₃ group, the R₃ group is attached to a carbon atom adjacent to a nitrogen attached to the pyridazinyl group, the carbon to which the R₃ group is attached is in the (R) configuration, and R₃ is -CH₃. In another embodiment, the Pyridazinylpiperazine Compound has only one R₃ group, the R₃ group is attached to a carbon atom adjacent to a nitrogen attached to the pyridazinyl group, the carbon to which the R₃ group is attached is in the (R) configuration, and R₃ is -CF₃. In another embodiment, the Pyridazinylpiperazine Compound has only one R₃ group, the R₃

group is attached to a carbon atom adjacent to a nitrogen attached to the pyridazinyl group, the carbon to which the R₃ group is attached is in the (R) configuration, and R₃ is -CH₂CH₃.

In another embodiment, the Pyridazinylpiperazine Compound has only one R₃ group, the R₃ group is attached to a carbon atom adjacent to a nitrogen atom attached to the -C(=O)-A-R₄, -C(=S)-A-R₄, phenethyl, or phenpropyl group, and the carbon to which the R₃ group is attached is in the (R) configuration. In another embodiment, the Pyridazinylpiperazine Compound has only one R₃ group, the R₃ group is attached to a carbon atom adjacent to a nitrogen attached to the -C(=O)-A-R₄, -C(=S)-A-R₄, phenethyl, or phenpropyl group, the carbon to which the R₃ group is attached is in the (R) configuration, and R₃ is -(C₁-C₄)alkyl unsubstituted or substituted with one or more halo groups. In another embodiment, the Pyridazinylpiperazine Compound has only one R₃ group, the R₃ group is attached to a carbon atom adjacent to a nitrogen attached to the -C(=O)-A-R₄, -C(=S)-A-R₄, phenethyl, or phenpropyl group, the carbon to which the R₃ group is attached is in the (R) configuration, and R₃ is -CH₃. In another embodiment, the Pyridazinylpiperazine Compound has only one R₃ group, the R₃ group is attached to a carbon atom adjacent to a nitrogen attached to the -C(=O)-A-R₄, -C(=S)-A-R₄, phenethyl, or phenpropyl group, the carbon to which the R₃ group is attached is in the (R) configuration, and R₃ is -CF₃. In another embodiment, the Pyridazinylpiperazine Compound has only one R₃ group, the R₃ group is attached to a carbon atom adjacent to a nitrogen attached to the -C(=O)-A-R₄, -C(=S)-A-R₄, phenethyl, or phenpropyl group, the carbon to which the R₃ group is attached is in the (R) configuration, and R₃ is -CH₂CH₃.

In another embodiment, the Pyridazinylpiperazine Compound has only one R₃ group, the R₃ group is attached to a carbon atom adjacent to a nitrogen atom attached to the pyridazinyl group, and the carbon to which the R₃ group is attached is in the (S) configuration. In another embodiment, the Pyridazinylpiperazine Compound has only one R₃ group, the R₃ group is attached to a carbon atom adjacent to a nitrogen attached to the pyridazinyl group, the carbon to which the R₃ group is attached is in the (S) configuration, and R₃ is -(C₁-C₄)alkyl unsubstituted or substituted with one or more halo groups. In another embodiment, the Pyridazinylpiperazine Compound has only one R₃ group, the R₃ group is attached to a carbon atom adjacent to a nitrogen attached to the pyridazinyl group, the carbon to which the R₃ group is attached is in the (S) configuration, and R₃ is -CH₃. In another embodiment, the Pyridazinylpiperazine Compound has only one R₃ group, the R₃ group is attached to a carbon atom adjacent to a nitrogen attached to the pyridazinyl group, the carbon to which the R₃ group is attached is in the (S) configuration, and R₃ is -CF₃. In another embodiment, the Pyridazinylpiperazine Compound has only one R₃ group, the R₃

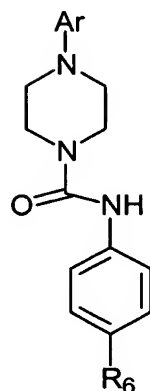
group is attached to a carbon atom adjacent to a nitrogen attached to the pyridazinyl group, the carbon to which the R₃ group is attached is in the (S) configuration, and R₃ is -CH₂CH₃.

In another embodiment, the Pyridazinylpiperazine Compound has only one R₃ group, the R₃ group is attached to a carbon atom adjacent to a nitrogen atom attached to the -C(=O)-A-R₄, -C(=S)-A-R₄, phenethyl, or phenpropyl group, and the carbon to which the R₃ group is attached is in the (S) configuration. In another embodiment, the Pyridazinylpiperazine Compound has only one R₃ group, the R₃ group is attached to a carbon atom adjacent to a nitrogen attached to the -C(=O)-A-R₄, -C(=S)-A-R₄, phenethyl, or phenpropyl group, the carbon to which the R₃ group is attached is in the (S) configuration, and R₃ is -(C₁-C₄)alkyl unsubstituted or substituted with one or more halo groups. In another embodiment, the Pyridazinylpiperazine Compound has only one R₃ group, the R₃ group is attached to a carbon atom adjacent to a nitrogen attached to the -C(=O)-A-R₄, -C(=S)-A-R₄, phenethyl, or phenpropyl group, the carbon to which the R₃ group is attached is in the (S) configuration, and R₃ is -CH₃. In another embodiment, the Pyridazinylpiperazine Compound has only one R₃ group, the R₃ group is attached to a carbon atom adjacent to a nitrogen attached to the -C(=O)-A-R₄, -C(=S)-A-R₄, phenethyl, or phenpropyl group, the carbon to which the R₃ group is attached is in the (S) configuration, and R₃ is -CF₃. In another embodiment, the Pyridazinylpiperazine Compound has only one R₃ group, the R₃ group is attached to a carbon atom adjacent to a nitrogen attached to the -C(=O)-A-R₄, -C(=S)-A-R₄, phenethyl, or phenpropyl group, the carbon to which the R₃ group is attached is in the (S) configuration, and R₃ is -CH₂CH₃.

In addition, one or more hydrogen, carbon or other atoms of a Pyridazinylpiperazine Compound can be replaced by an isotope of the hydrogen, carbon or other atoms. Such compounds, which are encompassed by the present invention, are useful as research and diagnostic tools in metabolism pharmacokinetic studies and in binding assays.

Illustrative Pyridazinylpiperazine Compounds are listed below in Tables I-XIV:

Table I



(VI)

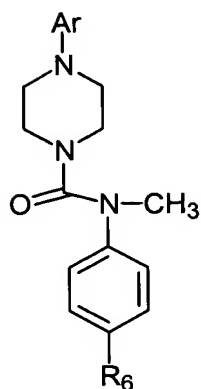
5 and pharmaceutically acceptable salts thereof, wherein:

<u>Compound</u>	<u>Ar</u>	<u>R₆</u>
A1	-3-(4-chloropyridazinyl)	-t-butyl
A2	-3-(4-chloropyridazinyl)	-iso-butyl
A3	-3-(4-chloropyridazinyl)	-sec-butyl
A4	-3-(4-chloropyridazinyl)	-cyclohexyl
A5	-3-(4-chloropyridazinyl)	-t-butoxy
A6	-3-(4-chloropyridazinyl)	-isopropoxy
A7	-3-(4-chloropyridazinyl)	-CF ₃
A8	-3-(4-chloropyridazinyl)	-CH ₂ CF ₃
A9	-3-(4-chloropyridazinyl)	-OCF ₃
A10	-3-(4-chloropyridazinyl)	-Cl
A11	-3-(4-chloropyridazinyl)	-Br
A12	-3-(4-chloropyridazinyl)	-I
A13	-3-(4-chloropyridazinyl)	-n-butyl
A14	-3-(4-chloropyridazinyl)	-n-propyl
A15	-3-(4-chloropyridazinyl)	-iso-propyl
A16	-3-(4-chloropyridazinyl)	-p-C ₆ H ₄ -C ₆ H ₅
A17	-3-(4-methylpyridazinyl)	-t-butyl
A18	-3-(4-methylpyridazinyl)	-iso-butyl

A19	-3-(4-methylpyridazinyl)	-sec-butyl
A20	-3-(4-methylpyridazinyl)	-cyclohexyl
A21	-3-(4-methylpyridazinyl)	-t-butoxy
A22	-3-(4-methylpyridazinyl)	-isopropoxy
A23	-3-(4-methylpyridazinyl)	-CF ₃
A24	-3-(4-methylpyridazinyl)	-CH ₂ CF ₃
A25	-3-(4-methylpyridazinyl)	-OCF ₃
A26	-3-(4-methylpyridazinyl)	-Cl
A27	-3-(4-methylpyridazinyl)	-Br
A28	-3-(4-methylpyridazinyl)	-I
A29	-3-(4-methylpyridazinyl)	-n-butyl
A30	-3-(4-methylpyridazinyl)	-n-propyl
A31	-3-(4-methylpyridazinyl)	-iso-propyl
A32	-3-(4-methylpyridazinyl)	-p-C ₆ H ₄ -C ₆ H ₅
A33	-3-(4-fluoropyridazinyl)	-t-butyl
A34	-3-(4-fluoropyridazinyl)	-iso-butyl
A35	-3-(4-fluoropyridazinyl)	-sec-butyl
A36	-3-(4-fluoropyridazinyl)	-cyclohexyl
A37	-3-(4-fluoropyridazinyl)	-t-butoxy
A38	-3-(4-fluoropyridazinyl)	-isopropoxy
A39	-3-(4-fluoropyridazinyl)	-CF ₃
A40	-3-(4-fluoropyridazinyl)	-CH ₂ CF ₃
A41	-3-(4-fluoropyridazinyl)	-OCF ₃
A42	-3-(4-fluoropyridazinyl)	-Cl
A43	-3-(4-fluoropyridazinyl)	-Br
A44	-3-(4-fluoropyridazinyl)	-I
A45	-3-(4-fluoropyridazinyl)	-n-butyl
A46	-3-(4-fluoropyridazinyl)	-n-propyl
A47	-3-(4-fluoropyridazinyl)	-iso-propyl
A48	-3-(4-fluoropyridazinyl)	-p-C ₆ H ₄ -C ₆ H ₅

A49	-3-(4-methyl-6-chloropyridazinyl)	-t-butyl
A50	-3-(4-methyl-6-chloropyridazinyl)	-iso-butyl
A51	-3-(4-methyl-6-chloropyridazinyl)	-sec-butyl
A52	-3-(4-methyl-6-chloropyridazinyl)	-cyclohexyl
A53	-3-(4-methyl-6-chloropyridazinyl)	-t-butoxy
A54	-3-(4-methyl-6-chloropyridazinyl)	-isopropoxy
A55	-3-(4-methyl-6-chloropyridazinyl)	-CF ₃
A56	-3-(4-methyl-6-chloropyridazinyl)	-CH ₂ CF ₃
A57	-3-(4-methyl-6-chloropyridazinyl)	-OCF ₃
A58	-3-(4-methyl-6-chloropyridazinyl)	-Cl
A59	-3-(4-methyl-6-chloropyridazinyl)	-Br
A60	-3-(4-methyl-6-chloropyridazinyl)	-I
A61	-3-(4-methyl-6-chloropyridazinyl)	-n-butyl
A62	-3-(4-methyl-6-chloropyridazinyl)	-n-propyl
A63	-3-(4-methyl-6-chloropyridazinyl)	-iso-propyl
A64	-3-(4-methyl-6-chloropyridazinyl)	-p-C ₆ H ₄ -C ₆ H ₅

Table II



and pharmaceutically acceptable salts thereof, wherein:

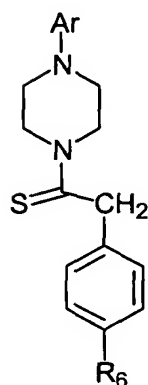
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<u>Compound</u>	<u>Ar</u>	<u>R₆</u>
B1	-3-(4-chloropyridazinyl)	-t-butyl
B2	-3-(4-chloropyridazinyl)	-iso-butyl
B3	-3-(4-chloropyridazinyl)	-sec-butyl
B4	-3-(4-chloropyridazinyl)	-cyclohexyl
B5	-3-(4-chloropyridazinyl)	-t-butoxy
B6	-3-(4-chloropyridazinyl)	-isopropoxy
B7	-3-(4-chloropyridazinyl)	-CF ₃
B8	-3-(4-chloropyridazinyl)	-CH ₂ CF ₃
B9	-3-(4-chloropyridazinyl)	-OCF ₃
B10	-3-(4-chloropyridazinyl)	-Cl
B11	-3-(4-chloropyridazinyl)	-Br
B12	-3-(4-chloropyridazinyl)	-I
B13	-3-(4-chloropyridazinyl)	-n-butyl
B14	-3-(4-chloropyridazinyl)	-n-propyl
B15	-3-(4-chloropyridazinyl)	-iso-propyl
B16	-3-(4-chloropyridazinyl)	-p-C ₆ H ₄ -C ₆ H ₅
B17	-3-(4-methylpyridazinyl)	-t-butyl
B18	-3-(4-methylpyridazinyl)	-iso-butyl

B19	-3-(4-methylpyridazinyl)	-sec-butyl
B20	-3-(4-methylpyridazinyl)	-cyclohexyl
B21	-3-(4-methylpyridazinyl)	-t-butoxy
B22	-3-(4-methylpyridazinyl)	-isopropoxy
B23	-3-(4-methylpyridazinyl)	-CF ₃
B24	-3-(4-methylpyridazinyl)	-CH ₂ CF ₃
B25	-3-(4-methylpyridazinyl)	-OCF ₃
B26	-3-(4-methylpyridazinyl)	-Cl
B27	-3-(4-methylpyridazinyl)	-Br
B28	-3-(4-methylpyridazinyl)	-I
B29	-3-(4-methylpyridazinyl)	-n-butyl
B30	-3-(4-methylpyridazinyl)	-n-propyl
B31	-3-(4-methylpyridazinyl)	-iso-propyl
B32	-3-(4-methylpyridazinyl)	-p-C ₆ H ₄ -C ₆ H ₅
B33	-3-(4-fluoropyridazinyl)	-t-butyl
B34	-3-(4-fluoropyridazinyl)	-iso-butyl
B35	-3-(4-fluoropyridazinyl)	-sec-butyl
B36	-3-(4-fluoropyridazinyl)	-cyclohexyl
B37	-3-(4-fluoropyridazinyl)	-t-butoxy
B38	-3-(4-fluoropyridazinyl)	-isopropoxy
B39	-3-(4-fluoropyridazinyl)	-CF ₃
B40	-3-(4-fluoropyridazinyl)	-CH ₂ CF ₃
B41	-3-(4-fluoropyridazinyl)	-OCF ₃
B42	-3-(4-fluoropyridazinyl)	-Cl
B43	-3-(4-fluoropyridazinyl)	-Br
B44	-3-(4-fluoropyridazinyl)	-I
B45	-3-(4-fluoropyridazinyl)	-n-butyl
B46	-3-(4-fluoropyridazinyl)	-n-propyl
B47	-3-(4-fluoropyridazinyl)	-iso-propyl
B48	-3-(4-fluoropyridazinyl)	-p-C ₆ H ₄ -C ₆ H ₅

B49	-3-(4-methyl-6-chloropyridazinyl)	-t-butyl
B50	-3-(4-methyl-6-chloropyridazinyl)	-iso-butyl
B51	-3-(4-methyl-6-chloropyridazinyl)	-sec-butyl
B52	-3-(4-methyl-6-chloropyridazinyl)	-cyclohexyl
B53	-3-(4-methyl-6-chloropyridazinyl)	-t-butoxy
B54	-3-(4-methyl-6-chloropyridazinyl)	-isopropoxy
B55	-3-(4-methyl-6-chloropyridazinyl)	-CF ₃
B56	-3-(4-methyl-6-chloropyridazinyl)	-CH ₂ CF ₃
B57	-3-(4-methyl-6-chloropyridazinyl)	-OCF ₃
B58	-3-(4-methyl-6-chloropyridazinyl)	-Cl
B59	-3-(4-methyl-6-chloropyridazinyl)	-Br
B60	-3-(4-methyl-6-chloropyridazinyl)	-I
B61	-3-(4-methyl-6-chloropyridazinyl)	-n-butyl
B62	-3-(4-methyl-6-chloropyridazinyl)	-n-propyl
B63	-3-(4-methyl-6-chloropyridazinyl)	-iso-propyl
B64	-3-(4-methyl-6-chloropyridazinyl)	-p-C ₆ H ₄ -C ₆ H ₅

Table III



(VIII)

and pharmaceutically acceptable salts thereof, wherein:

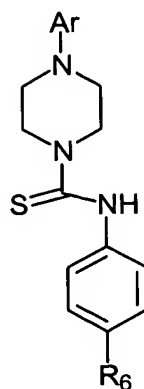
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<u>Compound</u>	<u>Ar</u>	<u>R₆</u>
C1	-3-(4-chloropyridazinyl)	-t-butyl
C2	-3-(4-chloropyridazinyl)	-iso-butyl
C3	-3-(4-chloropyridazinyl)	-sec-butyl
C4	-3-(4-chloropyridazinyl)	-cyclohexyl
C5	-3-(4-chloropyridazinyl)	-t-butoxy
C6	-3-(4-chloropyridazinyl)	-isopropoxy
C7	-3-(4-chloropyridazinyl)	-CF ₃
C8	-3-(4-chloropyridazinyl)	-CH ₂ CF ₃
C9	-3-(4-chloropyridazinyl)	-OCF ₃
C10	-3-(4-chloropyridazinyl)	-Cl
C11	-3-(4-chloropyridazinyl)	-Br
C12	-3-(4-chloropyridazinyl)	-I
C13	-3-(4-chloropyridazinyl)	-n-butyl
C14	-3-(4-chloropyridazinyl)	-n-propyl
C15	-3-(4-chloropyridazinyl)	-iso-propyl
C16	-3-(4-chloropyridazinyl)	-p-C ₆ H ₄ -C ₆ H ₅
C17	-3-(4-methylpyridazinyl)	-t-butyl
C18	-3-(4-methylpyridazinyl)	-iso-butyl

C19	-3-(4-methylpyridazinyl)	-sec-butyl
C20	-3-(4-methylpyridazinyl)	-cyclohexyl
C21	-3-(4-methylpyridazinyl)	-t-butoxy
C22	-3-(4-methylpyridazinyl)	-isopropoxy
C23	-3-(4-methylpyridazinyl)	-CF ₃
C24	-3-(4-methylpyridazinyl)	-CH ₂ CF ₃
C25	-3-(4-methylpyridazinyl)	-OCF ₃
C26	-3-(4-methylpyridazinyl)	-Cl
C27	-3-(4-methylpyridazinyl)	-Br
C28	-3-(4-methylpyridazinyl)	-I
C29	-3-(4-methylpyridazinyl)	-n-butyl
C30	-3-(4-methylpyridazinyl)	-n-propyl
C31	-3-(4-methylpyridazinyl)	-iso-propyl
C32	-3-(4-methylpyridazinyl)	-p-C ₆ H ₄ -C ₆ H ₅
C33	-3-(4-fluoropyridazinyl)	-t-butyl
C34	-3-(4-fluoropyridazinyl)	-iso-butyl
C35	-3-(4-fluoropyridazinyl)	-sec-butyl
C36	-3-(4-fluoropyridazinyl)	-cyclohexyl
C37	-3-(4-fluoropyridazinyl)	-t-butoxy
C38	-3-(4-fluoropyridazinyl)	-isopropoxy
C39	-3-(4-fluoropyridazinyl)	-CF ₃
C40	-3-(4-fluoropyridazinyl)	-CH ₂ CF ₃
C41	-3-(4-fluoropyridazinyl)	-OCF ₃
C42	-3-(4-fluoropyridazinyl)	-Cl
C43	-3-(4-fluoropyridazinyl)	-Br
C44	-3-(4-fluoropyridazinyl)	-I
C45	-3-(4-fluoropyridazinyl)	-n-butyl
C46	-3-(4-fluoropyridazinyl)	-n-propyl
C47	-3-(4-fluoropyridazinyl)	-iso-propyl
C48	-3-(4-fluoropyridazinyl)	-p-C ₆ H ₄ -C ₆ H ₅

C49	-3-(4-methyl-6-chloropyridazinyl)	-t-butyl
C50	-3-(4-methyl-6-chloropyridazinyl)	-iso-butyl
C51	-3-(4-methyl-6-chloropyridazinyl)	-sec-butyl
C52	-3-(4-methyl-6-chloropyridazinyl)	-cyclohexyl
C53	-3-(4-methyl-6-chloropyridazinyl)	-t-butoxy
C54	-3-(4-methyl-6-chloropyridazinyl)	-isopropoxy
C55	-3-(4-methyl-6-chloropyridazinyl)	-CF ₃
C56	-3-(4-methyl-6-chloropyridazinyl)	-CH ₂ CF ₃
C57	-3-(4-methyl-6-chloropyridazinyl)	-OCF ₃
C58	-3-(4-methyl-6-chloropyridazinyl)	-Cl
C59	-3-(4-methyl-6-chloropyridazinyl)	-Br
C60	-3-(4-methyl-6-chloropyridazinyl)	-I
C61	-3-(4-methyl-6-chloropyridazinyl)	-n-butyl
C62	-3-(4-methyl-6-chloropyridazinyl)	-n-propyl
C63	-3-(4-methyl-6-chloropyridazinyl)	-iso-propyl
C64	-3-(4-methyl-6-chloropyridazinyl)	-p-C ₆ H ₄ -C ₆ H ₅

Table IV



(IX)

and pharmaceutically acceptable salts thereof, wherein:

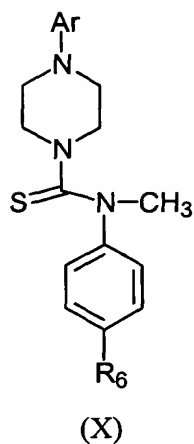
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<u>Compound</u>	<u>Ar</u>	<u>R₆</u>
D1	-3-(4-chloropyridazinyl)	-t-butyl
D2	-3-(4-chloropyridazinyl)	-iso-butyl
D3	-3-(4-chloropyridazinyl)	-sec-butyl
D4	-3-(4-chloropyridazinyl)	-cyclohexyl
D5	-3-(4-chloropyridazinyl)	-t-butoxy
D6	-3-(4-chloropyridazinyl)	-isopropoxy
D7	-3-(4-chloropyridazinyl)	-CF ₃
D8	-3-(4-chloropyridazinyl)	-CH ₂ CF ₃
D9	-3-(4-chloropyridazinyl)	-OCF ₃
D10	-3-(4-chloropyridazinyl)	-Cl
D11	-3-(4-chloropyridazinyl)	-Br
D12	-3-(4-chloropyridazinyl)	-I
D13	-3-(4-chloropyridazinyl)	-n-butyl
D14	-3-(4-chloropyridazinyl)	-n-propyl
D15	-3-(4-chloropyridazinyl)	-iso-propyl
D16	-3-(4-chloropyridazinyl)	-p-C ₆ H ₄ -C ₆ H ₅
D17	-3-(4-methylpyridazinyl)	-t-butyl
D18	-3-(4-methylpyridazinyl)	-iso-butyl

D19	-3-(4-methylpyridazinyl)	-sec-butyl
D20	-3-(4-methylpyridazinyl)	-cyclohexyl
D21	-3-(4-methylpyridazinyl)	-t-butoxy
D22	-3-(4-methylpyridazinyl)	-isopropoxy
D23	-3-(4-methylpyridazinyl)	-CF ₃
D24	-3-(4-methylpyridazinyl)	-CH ₂ CF ₃
D25	-3-(4-methylpyridazinyl)	-OCF ₃
D26	-3-(4-methylpyridazinyl)	-Cl
D27	-3-(4-methylpyridazinyl)	-Br
D28	-3-(4-methylpyridazinyl)	-I
D29	-3-(4-methylpyridazinyl)	-n-butyl
D30	-3-(4-methylpyridazinyl)	-n-propyl
D31	-3-(4-methylpyridazinyl)	-iso-propyl
D32	-3-(4-methylpyridazinyl)	-p-C ₆ H ₄ -C ₆ H ₅
D33	-3-(4-fluoropyridazinyl)	-t-butyl
D34	-3-(4-fluoropyridazinyl)	-iso-butyl
D35	-3-(4-fluoropyridazinyl)	-sec-butyl
D36	-3-(4-fluoropyridazinyl)	-cyclohexyl
D37	-3-(4-fluoropyridazinyl)	-t-butoxy
D38	-3-(4-fluoropyridazinyl)	-isopropoxy
D39	-3-(4-fluoropyridazinyl)	-CF ₃
D40	-3-(4-fluoropyridazinyl)	-CH ₂ CF ₃
D41	-3-(4-fluoropyridazinyl)	-OCF ₃
D42	-3-(4-fluoropyridazinyl)	-Cl
D43	-3-(4-fluoropyridazinyl)	-Br
D44	-3-(4-fluoropyridazinyl)	-I
D45	-3-(4-fluoropyridazinyl)	-n-butyl
D46	-3-(4-fluoropyridazinyl)	-n-propyl
D47	-3-(4-fluoropyridazinyl)	-iso-propyl
D48	-3-(4-fluoropyridazinyl)	-p-C ₆ H ₄ -C ₆ H ₅

D49	-3-(4-methyl-6-chloropyridazinyl)	-t-butyl
D50	-3-(4-methyl-6-chloropyridazinyl)	-iso-butyl
D51	-3-(4-methyl-6-chloropyridazinyl)	-sec-butyl
D52	-3-(4-methyl-6-chloropyridazinyl)	-cyclohexyl
D53	-3-(4-methyl-6-chloropyridazinyl)	-t-butoxy
D54	-3-(4-methyl-6-chloropyridazinyl)	-isopropoxy
D55	-3-(4-methyl-6-chloropyridazinyl)	-CF ₃
D56	-3-(4-methyl-6-chloropyridazinyl)	-CH ₂ CF ₃
D57	-3-(4-methyl-6-chloropyridazinyl)	-OCF ₃
D58	-3-(4-methyl-6-chloropyridazinyl)	-Cl
D59	-3-(4-methyl-6-chloropyridazinyl)	-Br
D60	-3-(4-methyl-6-chloropyridazinyl)	-I
D61	-3-(4-methyl-6-chloropyridazinyl)	-n-butyl
D62	-3-(4-methyl-6-chloropyridazinyl)	-n-propyl
D63	-3-(4-methyl-6-chloropyridazinyl)	-iso-propyl
D64	-3-(4-methyl-6-chloropyridazinyl)	-p-C ₆ H ₄ -C ₆ H ₅

Table V



and pharmaceutically acceptable salts thereof, wherein:

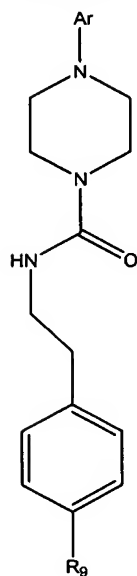
5

<u>Compound</u>	<u>Ar</u>	<u>R₆</u>
E1	-3-(4-chloropyridazinyl)	-t-butyl
E2	-3-(4-chloropyridazinyl)	-iso-butyl
E3	-3-(4-chloropyridazinyl)	-sec-butyl
E4	-3-(4-chloropyridazinyl)	-cyclohexyl
E5	-3-(4-chloropyridazinyl)	-t-butoxy
E6	-3-(4-chloropyridazinyl)	-isopropoxy
E7	-3-(4-chloropyridazinyl)	-CF ₃
E8	-3-(4-chloropyridazinyl)	-CH ₂ CF ₃
E9	-3-(4-chloropyridazinyl)	-OCF ₃
E10	-3-(4-chloropyridazinyl)	-Cl
E11	-3-(4-chloropyridazinyl)	-Br
E12	-3-(4-chloropyridazinyl)	-I
E13	-3-(4-chloropyridazinyl)	-n-butyl
E14	-3-(4-chloropyridazinyl)	-n-propyl
E15	-3-(4-chloropyridazinyl)	-iso-propyl
E16	-3-(4-chloropyridazinyl)	-p-C ₆ H ₄ -C ₆ H ₅
E17	-3-(4-methylpyridazinyl)	-t-butyl
E18	-3-(4-methylpyridazinyl)	-iso-butyl

E19	-3-(4-methylpyridazinyl)	-sec-butyl
E20	-3-(4-methylpyridazinyl)	-cyclohexyl
E21	-3-(4-methylpyridazinyl)	-t-butoxy
E22	-3-(4-methylpyridazinyl)	-isopropoxy
E23	-3-(4-methylpyridazinyl)	-CF ₃
E24	-3-(4-methylpyridazinyl)	-CH ₂ CF ₃
E25	-3-(4-methylpyridazinyl)	-OCF ₃
E26	-3-(4-methylpyridazinyl)	-Cl
E27	-3-(4-methylpyridazinyl)	-Br
E28	-3-(4-methylpyridazinyl)	-I
E29	-3-(4-methylpyridazinyl)	-n-butyl
E30	-3-(4-methylpyridazinyl)	-n-propyl
E31	-3-(4-methylpyridazinyl)	-iso-propyl
E32	-3-(4-methylpyridazinyl)	-p-C ₆ H ₄ -C ₆ H ₅
E33	-3-(4-fluoropyridazinyl)	-t-butyl
E34	-3-(4-fluoropyridazinyl)	-iso-butyl
E35	-3-(4-fluoropyridazinyl)	-sec-butyl
E36	-3-(4-fluoropyridazinyl)	-cyclohexyl
E37	-3-(4-fluoropyridazinyl)	-t-butoxy
E38	-3-(4-fluoropyridazinyl)	-isopropoxy
E39	-3-(4-fluoropyridazinyl)	-CF ₃
E40	-3-(4-fluoropyridazinyl)	-CH ₂ CF ₃
E41	-3-(4-fluoropyridazinyl)	-OCF ₃
E42	-3-(4-fluoropyridazinyl)	-Cl
E43	-3-(4-fluoropyridazinyl)	-Br
E44	-3-(4-fluoropyridazinyl)	-I
E45	-3-(4-fluoropyridazinyl)	-n-butyl
E46	-3-(4-fluoropyridazinyl)	-n-propyl
E47	-3-(4-fluoropyridazinyl)	-iso-propyl
E48	-3-(4-fluoropyridazinyl)	-p-C ₆ H ₄ -C ₆ H ₅

E49	-3-(4-methyl-6-chloropyridazinyl)	-t-butyl
E50	-3-(4-methyl-6-chloropyridazinyl)	-iso-butyl
E51	-3-(4-methyl-6-chloropyridazinyl)	-sec-butyl
E52	-3-(4-methyl-6-chloropyridazinyl)	-cyclohexyl
E53	-3-(4-methyl-6-chloropyridazinyl)	-t-butoxy
E54	-3-(4-methyl-6-chloropyridazinyl)	-isopropoxy
E55	-3-(4-methyl-6-chloropyridazinyl)	-CF ₃
E56	-3-(4-methyl-6-chloropyridazinyl)	-CH ₂ CF ₃
E57	-3-(4-methyl-6-chloropyridazinyl)	-OCF ₃
E58	-3-(4-methyl-6-chloropyridazinyl)	-Cl
E59	-3-(4-methyl-6-chloropyridazinyl)	-Br
E60	-3-(4-methyl-6-chloropyridazinyl)	-I
E61	-3-(4-methyl-6-chloropyridazinyl)	-n-butyl
E62	-3-(4-methyl-6-chloropyridazinyl)	-n-propyl
E63	-3-(4-methyl-6-chloropyridazinyl)	-iso-propyl
E64	-3-(4-methyl-6-chloropyridazinyl)	-p-C ₆ H ₄ -C ₆ H ₅

Table VI



(XI)

and pharmaceutically acceptable salts thereof, wherein:

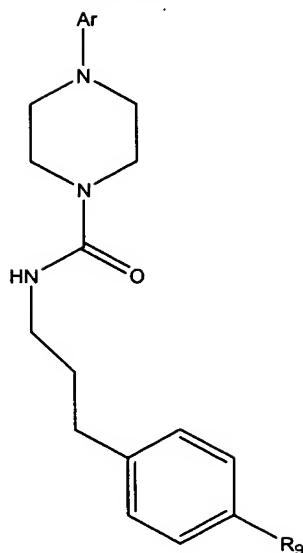
5

<u>Compound</u>	<u>Ar</u>	<u>R₆</u>
F1	-3-(4-chloropyridazinyl)	-t-butyl
F2	-3-(4-chloropyridazinyl)	-iso-butyl
F3	-3-(4-chloropyridazinyl)	-sec-butyl
F4	-3-(4-chloropyridazinyl)	-cyclohexyl
F5	-3-(4-chloropyridazinyl)	-t-butoxy
F6	-3-(4-chloropyridazinyl)	-isopropoxy
F7	-3-(4-chloropyridazinyl)	-CF ₃
F8	-3-(4-chloropyridazinyl)	-CH ₂ CF ₃
F9	-3-(4-chloropyridazinyl)	-OCF ₃
F10	-3-(4-chloropyridazinyl)	-Cl
F11	-3-(4-chloropyridazinyl)	-Br
F12	-3-(4-chloropyridazinyl)	-I
F13	-3-(4-chloropyridazinyl)	-n-butyl
F14	-3-(4-chloropyridazinyl)	-n-propyl
F15	-3-(4-chloropyridazinyl)	-iso-propyl
F16	-3-(4-chloropyridazinyl)	-p-C ₆ H ₄ -C ₆ H ₅

F17	-3-(4-methylpyridazinyl)	-t-butyl
F18	-3-(4-methylpyridazinyl)	-iso-butyl
F19	-3-(4-methylpyridazinyl)	-sec-butyl
F20	-3-(4-methylpyridazinyl)	-cyclohexyl
F21	-3-(4-methylpyridazinyl)	-t-butoxy
F22	-3-(4-methylpyridazinyl)	-isopropoxy
F23	-3-(4-methylpyridazinyl)	-CF ₃
F24	-3-(4-methylpyridazinyl)	-CH ₂ CF ₃
F25	-3-(4-methylpyridazinyl)	-OCF ₃
F26	-3-(4-methylpyridazinyl)	-Cl
F27	-3-(4-methylpyridazinyl)	-Br
F28	-3-(4-methylpyridazinyl)	-I
F29	-3-(4-methylpyridazinyl)	-n-butyl
F30	-3-(4-methylpyridazinyl)	-n-propyl
F31	-3-(4-methylpyridazinyl)	-iso-propyl
F32	-3-(4-methylpyridazinyl)	-p-C ₆ H ₄ -C ₆ H ₅
F33	-3-(4-fluoropyridazinyl)	-t-butyl
F34	-3-(4-fluoropyridazinyl)	-iso-butyl
F35	-3-(4-fluoropyridazinyl)	-sec-butyl
F36	-3-(4-fluoropyridazinyl)	-cyclohexyl
F37	-3-(4-fluoropyridazinyl)	-t-butoxy
F38	-3-(4-fluoropyridazinyl)	-isopropoxy
F39	-3-(4-fluoropyridazinyl)	-CF ₃
F40	-3-(4-fluoropyridazinyl)	-CH ₂ CF ₃
F41	-3-(4-fluoropyridazinyl)	-OCF ₃
F42	-3-(4-fluoropyridazinyl)	-Cl
F43	-3-(4-fluoropyridazinyl)	-Br
F44	-3-(4-fluoropyridazinyl)	-I
F45	-3-(4-fluoropyridazinyl)	-n-butyl
F46	-3-(4-fluoropyridazinyl)	-n-propyl

F47	-3-(4-fluoropyridazinyl)	-iso-propyl
F48	-3-(4-fluoropyridazinyl)	-p-C ₆ H ₄ -C ₆ H ₅
F49	-3-(4-methyl-6-chloropyridazinyl)	-t-butyl
F50	-3-(4-methyl-6-chloropyridazinyl)	-iso-butyl
F51	-3-(4-methyl-6-chloropyridazinyl)	-sec-butyl
F52	-3-(4-methyl-6-chloropyridazinyl)	-cyclohexyl
F53	-3-(4-methyl-6-chloropyridazinyl)	-t-butoxy
F54	-3-(4-methyl-6-chloropyridazinyl)	-isopropoxy
F55	-3-(4-methyl-6-chloropyridazinyl)	-CF ₃
F56	-3-(4-methyl-6-chloropyridazinyl)	-CH ₂ CF ₃
F57	-3-(4-methyl-6-chloropyridazinyl)	-OCF ₃
F58	-3-(4-methyl-6-chloropyridazinyl)	-Cl
F59	-3-(4-methyl-6-chloropyridazinyl)	-Br
F60	-3-(4-methyl-6-chloropyridazinyl)	-I
F61	-3-(4-methyl-6-chloropyridazinyl)	-n-butyl
F62	-3-(4-methyl-6-chloropyridazinyl)	-n-propyl
F63	-3-(4-methyl-6-chloropyridazinyl)	-iso-propyl
F64	-3-(4-methyl-6-chloropyridazinyl)	-p-C ₆ H ₄ -C ₆ H ₅

Table VII



(XII)

and pharmaceutically acceptable salts thereof, wherein:

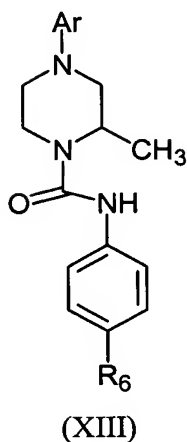
5

<u>Compound</u>	<u>Ar</u>	<u>R₆</u>
G1	-3-(4-chloropyridazinyl)	-t-butyl
G2	-3-(4-chloropyridazinyl)	-iso-butyl
G3	-3-(4-chloropyridazinyl)	-sec-butyl
G4	-3-(4-chloropyridazinyl)	-cyclohexyl
G5	-3-(4-chloropyridazinyl)	-t-butoxy
G6	-3-(4-chloropyridazinyl)	-isopropoxy
G7	-3-(4-chloropyridazinyl)	-CF ₃
G8	-3-(4-chloropyridazinyl)	-CH ₂ CF ₃
G9	-3-(4-chloropyridazinyl)	-OCF ₃
G10	-3-(4-chloropyridazinyl)	-Cl
G11	-3-(4-chloropyridazinyl)	-Br
G12	-3-(4-chloropyridazinyl)	-I
G13	-3-(4-chloropyridazinyl)	-n-butyl
G14	-3-(4-chloropyridazinyl)	-n-propyl
G15	-3-(4-chloropyridazinyl)	-iso-propyl
G16	-3-(4-chloropyridazinyl)	-p-C ₆ H ₄ -C ₆ H ₅

G17	-3-(4-methylpyridazinyl)	-t-butyl
G18	-3-(4-methylpyridazinyl)	-iso-butyl
G19	-3-(4-methylpyridazinyl)	-sec-butyl
G20	-3-(4-methylpyridazinyl)	-cyclohexyl
G21	-3-(4-methylpyridazinyl)	-t-butoxy
G22	-3-(4-methylpyridazinyl)	-isopropoxy
G23	-3-(4-methylpyridazinyl)	-CF ₃
G24	-3-(4-methylpyridazinyl)	-CH ₂ CF ₃
G25	-3-(4-methylpyridazinyl)	-OCF ₃
G26	-3-(4-methylpyridazinyl)	-Cl
G27	-3-(4-methylpyridazinyl)	-Br
G28	-3-(4-methylpyridazinyl)	-I
G29	-3-(4-methylpyridazinyl)	-n-butyl
G30	-3-(4-methylpyridazinyl)	-n-propyl
G31	-3-(4-methylpyridazinyl)	-iso-propyl
G32	-3-(4-methylpyridazinyl)	-p-C ₆ H ₄ -C ₆ H ₅
G33	-3-(4-fluoropyridazinyl)	-t-butyl
G34	-3-(4-fluoropyridazinyl)	-iso-butyl
G35	-3-(4-fluoropyridazinyl)	-sec-butyl
G36	-3-(4-fluoropyridazinyl)	-cyclohexyl
G37	-3-(4-fluoropyridazinyl)	-t-butoxy
G38	-3-(4-fluoropyridazinyl)	-isopropoxy
G39	-3-(4-fluoropyridazinyl)	-CF ₃
G40	-3-(4-fluoropyridazinyl)	-CH ₂ CF ₃
G41	-3-(4-fluoropyridazinyl)	-OCF ₃
G42	-3-(4-fluoropyridazinyl)	-Cl
G43	-3-(4-fluoropyridazinyl)	-Br
G44	-3-(4-fluoropyridazinyl)	-I
G45	-3-(4-fluoropyridazinyl)	-n-butyl
G46	-3-(4-fluoropyridazinyl)	-n-propyl

G47	-3-(4-fluoropyridazinyl)	-iso-propyl
G48	-3-(4-fluoropyridazinyl)	-p-C ₆ H ₄ -C ₆ H ₅
G49	-3-(4-methyl-6-chloropyridazinyl)	-t-butyl
G50	-3-(4-methyl-6-chloropyridazinyl)	-iso-butyl
G51	-3-(4-methyl-6-chloropyridazinyl)	-sec-butyl
G52	-3-(4-methyl-6-chloropyridazinyl)	-cyclohexyl
G53	-3-(4-methyl-6-chloropyridazinyl)	-t-butoxy
G54	-3-(4-methyl-6-chloropyridazinyl)	-isopropoxy
G55	-3-(4-methyl-6-chloropyridazinyl)	-CF ₃
G56	-3-(4-methyl-6-chloropyridazinyl)	-CH ₂ CF ₃
G57	-3-(4-methyl-6-chloropyridazinyl)	-OCF ₃
G58	-3-(4-methyl-6-chloropyridazinyl)	-Cl
G59	-3-(4-methyl-6-chloropyridazinyl)	-Br
G60	-3-(4-methyl-6-chloropyridazinyl)	-I
G61	-3-(4-methyl-6-chloropyridazinyl)	-n-butyl
G62	-3-(4-methyl-6-chloropyridazinyl)	-n-propyl
G63	-3-(4-methyl-6-chloropyridazinyl)	-iso-propyl
G64	-3-(4-methyl-6-chloropyridazinyl)	-p-C ₆ H ₄ -C ₆ H ₅

Table VIII



and pharmaceutically acceptable salts thereof, wherein:

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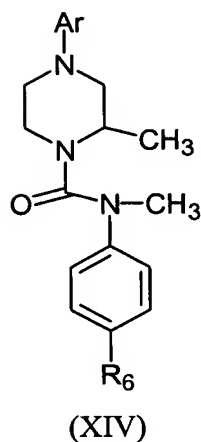
<u>Compound</u>	<u>Ar</u>	<u>R₆</u>
H1 (a) and (b)	-3-(4-chloropyridazinyl)	-t-butyl
H2 (a) and (b)	-3-(4-chloropyridazinyl)	-iso-butyl
H3 (a) and (b)	-3-(4-chloropyridazinyl)	-sec-butyl
H4 (a) and (b)	-3-(4-chloropyridazinyl)	-cyclohexyl
H5 (a) and (b)	-3-(4-chloropyridazinyl)	-t-butoxy
H6 (a) and (b)	-3-(4-chloropyridazinyl)	-isopropoxy
H7 (a) and (b)	-3-(4-chloropyridazinyl)	-CF ₃
H8 (a) and (b)	-3-(4-chloropyridazinyl)	-CH ₂ CF ₃
H9 (a) and (b)	-3-(4-chloropyridazinyl)	-OCF ₃
H10 (a) and (b)	-3-(4-chloropyridazinyl)	-Cl
H11 (a) and (b)	-3-(4-chloropyridazinyl)	-Br
H12 (a) and (b)	-3-(4-chloropyridazinyl)	-I
H13 (a) and (b)	-3-(4-chloropyridazinyl)	-n-butyl
H14 (a) and (b)	-3-(4-chloropyridazinyl)	-n-propyl
H15 (a) and (b)	-3-(4-chloropyridazinyl)	-iso-propyl
H16 (a) and (b)	-3-(4-chloropyridazinyl)	-p-C ₆ H ₄ -C ₆ H ₅
H17 (a) and (b)	-3-(4-methylpyridazinyl)	-t-butyl
H18 (a) and (b)	-3-(4-methylpyridazinyl)	-iso-butyl
H19 (a) and (b)	-3-(4-methylpyridazinyl)	-sec-butyl

H20 (a) and (b)	-3-(4-methylpyridazinyl)	-cyclohexyl
H21 (a) and (b)	-3-(4-methylpyridazinyl)	-t-butoxy
H22 (a) and (b)	-3-(4-methylpyridazinyl)	-isopropoxy
H23 (a) and (b)	-3-(4-methylpyridazinyl)	-CF ₃
H24 (a) and (b)	-3-(4-methylpyridazinyl)	-CH ₂ CF ₃
H25 (a) and (b)	-3-(4-methylpyridazinyl)	-OCF ₃
H26 (a) and (b)	-3-(4-methylpyridazinyl)	-Cl
H27 (a) and (b)	-3-(4-methylpyridazinyl)	-Br
H28 (a) and (b)	-3-(4-methylpyridazinyl)	-I
H29 (a) and (b)	-3-(4-methylpyridazinyl)	-n-butyl
H30 (a) and (b)	-3-(4-methylpyridazinyl)	-n-propyl
H31 (a) and (b)	-3-(4-methylpyridazinyl)	-iso-propyl
H32 (a) and (b)	-3-(4-methylpyridazinyl)	-p-C ₆ H ₄ -C ₆ H ₅
H33 (a) and (b)	-3-(4-fluoropyridazinyl)	-t-butyl
H34 (a) and (b)	-3-(4-fluoropyridazinyl)	-iso-butyl
H35 (a) and (b)	-3-(4-fluoropyridazinyl)	-sec-butyl
H36 (a) and (b)	-3-(4-fluoropyridazinyl)	-cyclohexyl
H37 (a) and (b)	-3-(4-fluoropyridazinyl)	-t-butoxy
H38 (a) and (b)	-3-(4-fluoropyridazinyl)	-isopropoxy
H39 (a) and (b)	-3-(4-fluoropyridazinyl)	-CF ₃
H40 (a) and (b)	-3-(4-fluoropyridazinyl)	-CH ₂ CF ₃
H41 (a) and (b)	-3-(4-fluoropyridazinyl)	-OCF ₃
H42 (a) and (b)	-3-(4-fluoropyridazinyl)	-Cl
H43 (a) and (b)	-3-(4-fluoropyridazinyl)	-Br
H44 (a) and (b)	-3-(4-fluoropyridazinyl)	-I
H45 (a) and (b)	-3-(4-fluoropyridazinyl)	-n-butyl
H46 (a) and (b)	-3-(4-fluoropyridazinyl)	-n-propyl
H47 (a) and (b)	-3-(4-fluoropyridazinyl)	-iso-propyl
H48 (a) and (b)	-3-(4-fluoropyridazinyl)	-p-C ₆ H ₄ -C ₆ H ₅
H49 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-t-butyl

H50 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-iso-butyl
H51 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-sec-butyl
H52 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-cyclohexyl
H53 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-t-butoxy
H54 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-isopropoxy
H55 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-CF ₃
H56 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-CH ₂ CF ₃
H57 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-OCF ₃
H58 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-Cl
H59 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-Br
H60 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-I
H61 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-n-butyl
H62 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-n-propyl
H63 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-iso-propyl
H64 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-p-C ₆ H ₄ -C ₆ H ₅

wherein “(a)” means that the carbon atom of the piperazino group to which the methyl group is attached is in the R configuration and “(b)” means that the carbon atom of the piperazino group to which the methyl group is attached is in the S configuration.

Table IX



and pharmaceutically acceptable salts thereof, wherein:

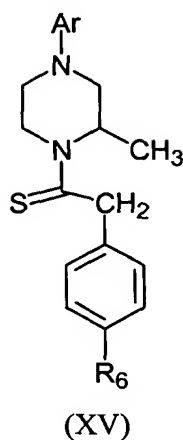
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<u>Compound</u>	<u>Ar</u>	<u>R₆</u>
I1 (a) and (b)	-3-(4-chloropyridazinyl)	-t-butyl
I2 (a) and (b)	-3-(4-chloropyridazinyl)	-iso-butyl
I3 (a) and (b)	-3-(4-chloropyridazinyl)	-sec-butyl
I4 (a) and (b)	-3-(4-chloropyridazinyl)	-cyclohexyl
I5 (a) and (b)	-3-(4-chloropyridazinyl)	-t-butoxy
I6 (a) and (b)	-3-(4-chloropyridazinyl)	-isopropoxy
I7 (a) and (b)	-3-(4-chloropyridazinyl)	-CF ₃
I8 (a) and (b)	-3-(4-chloropyridazinyl)	-CH ₂ CF ₃
I9 (a) and (b)	-3-(4-chloropyridazinyl)	-OCF ₃
I10 (a) and (b)	-3-(4-chloropyridazinyl)	-Cl
I11 (a) and (b)	-3-(4-chloropyridazinyl)	-Br
I12 (a) and (b)	-3-(4-chloropyridazinyl)	-I
I13 (a) and (b)	-3-(4-chloropyridazinyl)	-n-butyl
I14 (a) and (b)	-3-(4-chloropyridazinyl)	-n-propyl
I15 (a) and (b)	-3-(4-chloropyridazinyl)	-iso-propyl
I16 (a) and (b)	-3-(4-chloropyridazinyl)	-p-C ₆ H ₄ -C ₆ H ₅
I17 (a) and (b)	-3-(4-methylpyridazinyl)	-t-butyl

I18 (a) and (b)	-3-(4-methylpyridazinyl)	-iso-butyl
I19 (a) and (b)	-3-(4-methylpyridazinyl)	-sec-butyl
I20 (a) and (b)	-3-(4-methylpyridazinyl)	-cyclohexyl
I21 (a) and (b)	-3-(4-methylpyridazinyl)	-t-butoxy
I22 (a) and (b)	-3-(4-methylpyridazinyl)	-isopropoxy
I23 (a) and (b)	-3-(4-methylpyridazinyl)	-CF ₃
I24 (a) and (b)	-3-(4-methylpyridazinyl)	-CH ₂ CF ₃
I25 (a) and (b)	-3-(4-methylpyridazinyl)	-OCF ₃
I26 (a) and (b)	-3-(4-methylpyridazinyl)	-Cl
I27 (a) and (b)	-3-(4-methylpyridazinyl)	-Br
I28 (a) and (b)	-3-(4-methylpyridazinyl)	-I
I29 (a) and (b)	-3-(4-methylpyridazinyl)	-n-butyl
I30 (a) and (b)	-3-(4-methylpyridazinyl)	-n-propyl
I31 (a) and (b)	-3-(4-methylpyridazinyl)	-iso-propyl
I32 (a) and (b)	-3-(4-methylpyridazinyl)	-p-C ₆ H ₄ -C ₆ H ₅
I33 (a) and (b)	-3-(4-fluoropyridazinyl)	-t-butyl
I34 (a) and (b)	-3-(4-fluoropyridazinyl)	-iso-butyl
I35 (a) and (b)	-3-(4-fluoropyridazinyl)	-sec-butyl
I36 (a) and (b)	-3-(4-fluoropyridazinyl)	-cyclohexyl
I37 (a) and (b)	-3-(4-fluoropyridazinyl)	-t-butoxy
I38 (a) and (b)	-3-(4-fluoropyridazinyl)	-isopropoxy
I39 (a) and (b)	-3-(4-fluoropyridazinyl)	-CF ₃
I40 (a) and (b)	-3-(4-fluoropyridazinyl)	-CH ₂ CF ₃
I41 (a) and (b)	-3-(4-fluoropyridazinyl)	-OCF ₃
I42 (a) and (b)	-3-(4-fluoropyridazinyl)	-Cl
I43 (a) and (b)	-3-(4-fluoropyridazinyl)	-Br
I44 (a) and (b)	-3-(4-fluoropyridazinyl)	-I

I45 (a) and (b)	-3-(4-fluoropyridazinyl)	-n-butyl
I46 (a) and (b)	-3-(4-fluoropyridazinyl)	-n-propyl
I47 (a) and (b)	-3-(4-fluoropyridazinyl)	-iso-propyl
I48 (a) and (b)	-3-(4-fluoropyridazinyl)	-p-C ₆ H ₄ -C ₆ H ₅
I49 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-t-butyl
I50 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-iso-butyl
I51 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-sec-butyl
I52 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-cyclohexyl
I53 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-t-butoxy
I54 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-isopropoxy
I55 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-CF ₃
I56 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-CH ₂ CF ₃
I57 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-OCF ₃
I58 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-Cl
I59 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-Br
I60 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-I
I61 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-n-butyl
I62 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-n-propyl
I63 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-iso-propyl
I64 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-p-C ₆ H ₄ -C ₆ H ₅

wherein “(a)” means that the carbon atom of the piperazino group to which the methyl group is attached is in the R configuration and “(b)” means that the carbon atom of the piperazino group to which the methyl group is attached is in the S configuration.

Table X

and pharmaceutically acceptable salts thereof, wherein:

5

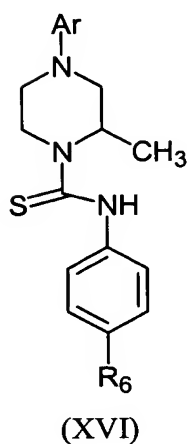
<u>Compound</u>	<u>Ar</u>	<u>R₆</u>
J1 (a) and (b)	-3-(4-chloropyridazinyl)	-t-butyl
J2 (a) and (b)	-3-(4-chloropyridazinyl)	-iso-butyl
J3 (a) and (b)	-3-(4-chloropyridazinyl)	-sec-butyl
J4 (a) and (b)	-3-(4-chloropyridazinyl)	-cyclohexyl
J5 (a) and (b)	-3-(4-chloropyridazinyl)	-t-butoxy
J6 (a) and (b)	-3-(4-chloropyridazinyl)	-isopropoxy
J7 (a) and (b)	-3-(4-chloropyridazinyl)	-CF ₃
J8 (a) and (b)	-3-(4-chloropyridazinyl)	-CH ₂ CF ₃
J9 (a) and (b)	-3-(4-chloropyridazinyl)	-OCF ₃
J10 (a) and (b)	-3-(4-chloropyridazinyl)	-Cl
J11 (a) and (b)	-3-(4-chloropyridazinyl)	-Br
J12 (a) and (b)	-3-(4-chloropyridazinyl)	-I
J13 (a) and (b)	-3-(4-chloropyridazinyl)	-n-butyl
J14 (a) and (b)	-3-(4-chloropyridazinyl)	-n-propyl
J15 (a) and (b)	-3-(4-chloropyridazinyl)	-iso-propyl
J16 (a) and (b)	-3-(4-chloropyridazinyl)	-p-C ₆ H ₄ -C ₆ H ₅
J17 (a) and (b)	-3-(4-methylpyridazinyl)	-t-butyl

J18 (a) and (b)	-3-(4-methylpyridazinyl)	-iso-butyl
J19 (a) and (b)	-3-(4-methylpyridazinyl)	-sec-butyl
J20 (a) and (b)	-3-(4-methylpyridazinyl)	-cyclohexyl
J21 (a) and (b)	-3-(4-methylpyridazinyl)	-t-butoxy
J22 (a) and (b)	-3-(4-methylpyridazinyl)	-isopropoxy
J23 (a) and (b)	-3-(4-methylpyridazinyl)	-CF ₃
J24 (a) and (b)	-3-(4-methylpyridazinyl)	-CH ₂ CF ₃
J25 (a) and (b)	-3-(4-methylpyridazinyl)	-OCF ₃
J26 (a) and (b)	-3-(4-methylpyridazinyl)	-Cl
J27 (a) and (b)	-3-(4-methylpyridazinyl)	-Br
J28 (a) and (b)	-3-(4-methylpyridazinyl)	-I
J29 (a) and (b)	-3-(4-methylpyridazinyl)	-n-butyl
J30 (a) and (b)	-3-(4-methylpyridazinyl)	-n-propyl
J31 (a) and (b)	-3-(4-methylpyridazinyl)	-iso-propyl
J32 (a) and (b)	-3-(4-methylpyridazinyl)	-p-C ₆ H ₄ -C ₆ H ₅
J33 (a) and (b)	-3-(4-fluoropyridazinyl)	-t-butyl
J34 (a) and (b)	-3-(4-fluoropyridazinyl)	-iso-butyl
J35 (a) and (b)	-3-(4-fluoropyridazinyl)	-sec-butyl
J36 (a) and (b)	-3-(4-fluoropyridazinyl)	-cyclohexyl
J37 (a) and (b)	-3-(4-fluoropyridazinyl)	-t-butoxy
J38 (a) and (b)	-3-(4-fluoropyridazinyl)	-isopropoxy
J39 (a) and (b)	-3-(4-fluoropyridazinyl)	-CF ₃
J40 (a) and (b)	-3-(4-fluoropyridazinyl)	-CH ₂ CF ₃
J41 (a) and (b)	-3-(4-fluoropyridazinyl)	-OCF ₃
J42 (a) and (b)	-3-(4-fluoropyridazinyl)	-Cl
J43 (a) and (b)	-3-(4-fluoropyridazinyl)	-Br
J44 (a) and (b)	-3-(4-fluoropyridazinyl)	-I

J45 (a) and (b)	-3-(4-fluoropyridazinyl)	-n-butyl
J46 (a) and (b)	-3-(4-fluoropyridazinyl)	-n-propyl
J47 (a) and (b)	-3-(4-fluoropyridazinyl)	-iso-propyl
J48 (a) and (b)	-3-(4-fluoropyridazinyl)	-p-C ₆ H ₄ -C ₆ H ₅
J49 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-t-butyl
J50 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-iso-butyl
J51 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-sec-butyl
J52 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-cyclohexyl
J53 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-t-butoxy
J54 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-isopropoxy
J55 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-CF ₃
J56 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-CH ₂ CF ₃
J57 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-OCF ₃
J58 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-Cl
J59 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-Br
J60 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-I
J61 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-n-butyl
J62 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-n-propyl
J63 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-iso-propyl
J64 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-p-C ₆ H ₄ -C ₆ H ₅

wherein “(a)” means that the carbon atom of the piperazino group to which the methyl group is attached is in the R configuration and “(b)” means that the carbon atom of the piperazino group to which the methyl group is attached is in the S configuration.

Table XI



and pharmaceutically acceptable salts thereof, wherein:

5

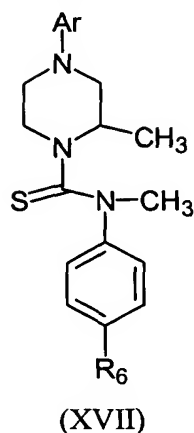
<u>Compound</u>	<u>Ar</u>	<u>R₆</u>
K1 (a) and (b)	-3-(4-chloropyridazinyl)	-t-butyl
K2 (a) and (b)	-3-(4-chloropyridazinyl)	-iso-butyl
K3 (a) and (b)	-3-(4-chloropyridazinyl)	-sec-butyl
K4 (a) and (b)	-3-(4-chloropyridazinyl)	-cyclohexyl
K5 (a) and (b)	-3-(4-chloropyridazinyl)	-t-butoxy
K6 (a) and (b)	-3-(4-chloropyridazinyl)	-isopropoxy
K7 (a) and (b)	-3-(4-chloropyridazinyl)	-CF ₃
K8 (a) and (b)	-3-(4-chloropyridazinyl)	-CH ₂ CF ₃
K9 (a) and (b)	-3-(4-chloropyridazinyl)	-OCF ₃
K10 (a) and (b)	-3-(4-chloropyridazinyl)	-Cl
K11 (a) and (b)	-3-(4-chloropyridazinyl)	-Br
K12 (a) and (b)	-3-(4-chloropyridazinyl)	-I
K13 (a) and (b)	-3-(4-chloropyridazinyl)	-n-butyl
K14 (a) and (b)	-3-(4-chloropyridazinyl)	-n-propyl
K15 (a) and (b)	-3-(4-chloropyridazinyl)	-iso-propyl
K16 (a) and (b)	-3-(4-chloropyridazinyl)	-p-C ₆ H ₄ -C ₆ H ₅
K17 (a) and (b)	-3-(4-methylpyridazinyl)	-t-butyl

K18 (a) and (b)	-3-(4-methylpyridazinyl)	-iso-butyl
K19 (a) and (b)	-3-(4-methylpyridazinyl)	-sec-butyl
K20 (a) and (b)	-3-(4-methylpyridazinyl)	-cyclohexyl
K21 (a) and (b)	-3-(4-methylpyridazinyl)	-t-butoxy
K22 (a) and (b)	-3-(4-methylpyridazinyl)	-isopropoxy
K23 (a) and (b)	-3-(4-methylpyridazinyl)	-CF ₃
K24 (a) and (b)	-3-(4-methylpyridazinyl)	-CH ₂ CF ₃
K25 (a) and (b)	-3-(4-methylpyridazinyl)	-OCF ₃
K26 (a) and (b)	-3-(4-methylpyridazinyl)	-Cl
K27 (a) and (b)	-3-(4-methylpyridazinyl)	-Br
K28 (a) and (b)	-3-(4-methylpyridazinyl)	-I
K29 (a) and (b)	-3-(4-methylpyridazinyl)	-n-butyl
K30 (a) and (b)	-3-(4-methylpyridazinyl)	-n-propyl
K31 (a) and (b)	-3-(4-methylpyridazinyl)	-iso-propyl
K32 (a) and (b)	-3-(4-methylpyridazinyl)	-p-C ₆ H ₄ -C ₆ H ₅
K33 (a) and (b)	-3-(4-fluoropyridazinyl)	-t-butyl
K34 (a) and (b)	-3-(4-fluoropyridazinyl)	-iso-butyl
K35 (a) and (b)	-3-(4-fluoropyridazinyl)	-sec-butyl
K36 (a) and (b)	-3-(4-fluoropyridazinyl)	-cyclohexyl
K37 (a) and (b)	-3-(4-fluoropyridazinyl)	-t-butoxy
K38 (a) and (b)	-3-(4-fluoropyridazinyl)	-isopropoxy
K39 (a) and (b)	-3-(4-fluoropyridazinyl)	-CF ₃
K40 (a) and (b)	-3-(4-fluoropyridazinyl)	-CH ₂ CF ₃
K41 (a) and (b)	-3-(4-fluoropyridazinyl)	-OCF ₃
K42 (a) and (b)	-3-(4-fluoropyridazinyl)	-Cl
K43 (a) and (b)	-3-(4-fluoropyridazinyl)	-Br
K44 (a) and (b)	-3-(4-fluoropyridazinyl)	-I

K45 (a) and (b)	-3-(4-fluoropyridazinyl)	-n-butyl
K46 (a) and (b)	-3-(4-fluoropyridazinyl)	-n-propyl
K47 (a) and (b)	-3-(4-fluoropyridazinyl)	-iso-propyl
K48 (a) and (b)	-3-(4-fluoropyridazinyl)	-p-C ₆ H ₄ -C ₆ H ₅
K49 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-t-butyl
K50 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-iso-butyl
K51 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-sec-butyl
K52 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-cyclohexyl
K53 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-t-butoxy
K54 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-isopropoxy
K55 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-CF ₃
K56 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-CH ₂ CF ₃
K57 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-OCF ₃
K58 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-Cl
K59 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-Br
K60 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-I
K61 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-n-butyl
K62 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-n-propyl
K63 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-iso-propyl
K64 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-p-C ₆ H ₄ -C ₆ H ₅

wherein “(a)” means that the carbon atom of the piperazino group to which the methyl group is attached is in the R configuration and “(b)” means that the carbon atom of the piperazino group to which the methyl group is attached is in the S configuration.

Table XII



and pharmaceutically acceptable salts thereof, wherein:

5

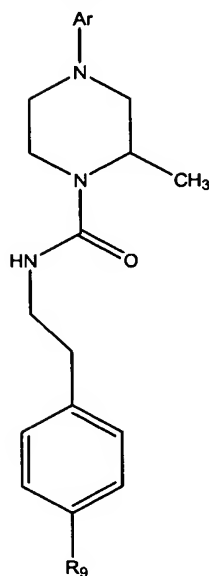
<u>Compound</u>	<u>Ar</u>	<u>R₆</u>
L1 (a) and (b)	-3-(4-chloropyridazinyl)	-t-butyl
L2 (a) and (b)	-3-(4-chloropyridazinyl)	-iso-butyl
L3 (a) and (b)	-3-(4-chloropyridazinyl)	-sec-butyl
L4 (a) and (b)	-3-(4-chloropyridazinyl)	-cyclohexyl
L5 (a) and (b)	-3-(4-chloropyridazinyl)	-t-butoxy
L6 (a) and (b)	-3-(4-chloropyridazinyl)	-isopropoxy
L7 (a) and (b)	-3-(4-chloropyridazinyl)	-CF ₃
L8 (a) and (b)	-3-(4-chloropyridazinyl)	-CH ₂ CF ₃
L9 (a) and (b)	-3-(4-chloropyridazinyl)	-OCF ₃
L10 (a) and (b)	-3-(4-chloropyridazinyl)	-Cl
L11 (a) and (b)	-3-(4-chloropyridazinyl)	-Br
L12 (a) and (b)	-3-(4-chloropyridazinyl)	-I
L13 (a) and (b)	-3-(4-chloropyridazinyl)	-n-butyl
L14 (a) and (b)	-3-(4-chloropyridazinyl)	-n-propyl
L15 (a) and (b)	-3-(4-chloropyridazinyl)	-iso-propyl
L16 (a) and (b)	-3-(4-chloropyridazinyl)	-p-C ₆ H ₄ -C ₆ H ₅
L17 (a) and (b)	-3-(4-methylpyridazinyl)	-t-butyl

L18 (a) and (b)	-3-(4-methylpyridazinyl)	-iso-butyl
L19 (a) and (b)	-3-(4-methylpyridazinyl)	-sec-butyl
L20 (a) and (b)	-3-(4-methylpyridazinyl)	-cyclohexyl
L21 (a) and (b)	-3-(4-methylpyridazinyl)	-t-butoxy
L22 (a) and (b)	-3-(4-methylpyridazinyl)	-isopropoxy
L23 (a) and (b)	-3-(4-methylpyridazinyl)	-CF ₃
L24 (a) and (b)	-3-(4-methylpyridazinyl)	-CH ₂ CF ₃
L25 (a) and (b)	-3-(4-methylpyridazinyl)	-OCF ₃
L26 (a) and (b)	-3-(4-methylpyridazinyl)	-Cl
L27 (a) and (b)	-3-(4-methylpyridazinyl)	-Br
L28 (a) and (b)	-3-(4-methylpyridazinyl)	-I
L29 (a) and (b)	-3-(4-methylpyridazinyl)	-n-butyl
L30 (a) and (b)	-3-(4-methylpyridazinyl)	-n-propyl
L31 (a) and (b)	-3-(4-methylpyridazinyl)	-iso-propyl
L32 (a) and (b)	-3-(4-methylpyridazinyl)	-p-C ₆ H ₄ -C ₆ H ₅
L33 (a) and (b)	-3-(4-fluoropyridazinyl)	-t-butyl
L34 (a) and (b)	-3-(4-fluoropyridazinyl)	-iso-butyl
L35 (a) and (b)	-3-(4-fluoropyridazinyl)	-sec-butyl
L36 (a) and (b)	-3-(4-fluoropyridazinyl)	-cyclohexyl
L37 (a) and (b)	-3-(4-fluoropyridazinyl)	-t-butoxy
L38 (a) and (b)	-3-(4-fluoropyridazinyl)	-isopropoxy
L39 (a) and (b)	-3-(4-fluoropyridazinyl)	-CF ₃
L40 (a) and (b)	-3-(4-fluoropyridazinyl)	-CH ₂ CF ₃
L41 (a) and (b)	-3-(4-fluoropyridazinyl)	-OCF ₃
L42 (a) and (b)	-3-(4-fluoropyridazinyl)	-Cl
L43 (a) and (b)	-3-(4-fluoropyridazinyl)	-Br
L44 (a) and (b)	-3-(4-fluoropyridazinyl)	-I

L45 (a) and (b)	-3-(4-fluoropyridazinyl)	-n-butyl
L46 (a) and (b)	-3-(4-fluoropyridazinyl)	-n-propyl
L47 (a) and (b)	-3-(4-fluoropyridazinyl)	-iso-propyl
L48 (a) and (b)	-3-(4-fluoropyridazinyl)	-p-C ₆ H ₄ -C ₆ H ₅
L49 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-t-butyl
L50 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-iso-butyl
L51 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-sec-butyl
L52 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-cyclohexyl
L53 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-t-butoxy
L54 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-isopropoxy
L55 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-CF ₃
L56 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-CH ₂ CF ₃
L57 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-OCF ₃
L58 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-Cl
L59 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-Br
L60 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-I
L61 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-n-butyl
L62 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-n-propyl
L63 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-iso-propyl
L64 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-p-C ₆ H ₄ -C ₆ H ₅

wherein “(a)” means that the carbon atom of the piperazino group to which the methyl group is attached is in the R configuration and “(b)” means that the carbon atom of the piperazino group to which the methyl group is attached is in the S configuration.

Table XIII



(XVIII)

and pharmaceutically acceptable salts thereof, wherein:

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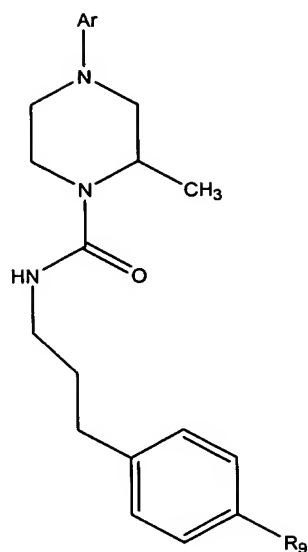
<u>Compound</u>	<u>Ar</u>	<u>R₆</u>
M1 (a) and (b)	-3-(4-chloropyridazinyl)	-t-butyl
M2 (a) and (b)	-3-(4-chloropyridazinyl)	-iso-butyl
M3 (a) and (b)	-3-(4-chloropyridazinyl)	-sec-butyl
M4 (a) and (b)	-3-(4-chloropyridazinyl)	-cyclohexyl
M5 (a) and (b)	-3-(4-chloropyridazinyl)	-t-butoxy
M6 (a) and (b)	-3-(4-chloropyridazinyl)	-isopropoxy
M7 (a) and (b)	-3-(4-chloropyridazinyl)	-CF ₃
M8 (a) and (b)	-3-(4-chloropyridazinyl)	-CH ₂ CF ₃
M9 (a) and (b)	-3-(4-chloropyridazinyl)	-OCF ₃
M10 (a) and (b)	-3-(4-chloropyridazinyl)	-Cl
M11 (a) and (b)	-3-(4-chloropyridazinyl)	-Br
M12 (a) and (b)	-3-(4-chloropyridazinyl)	-I
M13 (a) and (b)	-3-(4-chloropyridazinyl)	-n-butyl
M14 (a) and (b)	-3-(4-chloropyridazinyl)	-n-propyl

M15 (a) and (b)	-3-(4-chloropyridazinyl)	-iso-propyl
M16 (a) and (b)	-3-(4-chloropyridazinyl)	-p-C ₆ H ₄ -C ₆ H ₅
M17 (a) and (b)	-3-(4-methylpyridazinyl)	-t-butyl
M18 (a) and (b)	-3-(4-methylpyridazinyl)	-iso-butyl
M19 (a) and (b)	-3-(4-methylpyridazinyl)	-sec-butyl
M20 (a) and (b)	-3-(4-methylpyridazinyl)	-cyclohexyl
M21 (a) and (b)	-3-(4-methylpyridazinyl)	-t-butoxy
M22 (a) and (b)	-3-(4-methylpyridazinyl)	-isopropoxy
M23 (a) and (b)	-3-(4-methylpyridazinyl)	-CF ₃
M24 (a) and (b)	-3-(4-methylpyridazinyl)	-CH ₂ CF ₃
M25 (a) and (b)	-3-(4-methylpyridazinyl)	-OCF ₃
M26 (a) and (b)	-3-(4-methylpyridazinyl)	-Cl
M27 (a) and (b)	-3-(4-methylpyridazinyl)	-Br
M28 (a) and (b)	-3-(4-methylpyridazinyl)	-I
M29 (a) and (b)	-3-(4-methylpyridazinyl)	-n-butyl
M30 (a) and (b)	-3-(4-methylpyridazinyl)	-n-propyl
M31 (a) and (b)	-3-(4-methylpyridazinyl)	-iso-propyl
M32 (a) and (b)	-3-(4-methylpyridazinyl)	-p-C ₆ H ₄ -C ₆ H ₅
M33 (a) and (b)	-3-(4-fluoropyridazinyl)	-t-butyl
M34 (a) and (b)	-3-(4-fluoropyridazinyl)	-iso-butyl
M35 (a) and (b)	-3-(4-fluoropyridazinyl)	-sec-butyl
M36 (a) and (b)	-3-(4-fluoropyridazinyl)	-cyclohexyl
M37 (a) and (b)	-3-(4-fluoropyridazinyl)	-t-butoxy
M38 (a) and (b)	-3-(4-fluoropyridazinyl)	-isopropoxy
M39 (a) and (b)	-3-(4-fluoropyridazinyl)	-CF ₃
M40 (a) and (b)	-3-(4-fluoropyridazinyl)	-CH ₂ CF ₃
M41 (a) and (b)	-3-(4-fluoropyridazinyl)	-OCF ₃

M42 (a) and (b)	-3-(4-fluoropyridazinyl)	-Cl
M43 (a) and (b)	-3-(4-fluoropyridazinyl)	-Br
M44 (a) and (b)	-3-(4-fluoropyridazinyl)	-I
M45 (a) and (b)	-3-(4-fluoropyridazinyl)	-n-butyl
M46 (a) and (b)	-3-(4-fluoropyridazinyl)	-n-propyl
M47 (a) and (b)	-3-(4-fluoropyridazinyl)	-iso-propyl
M48 (a) and (b)	-3-(4-fluoropyridazinyl)	-p-C ₆ H ₄ -C ₆ H ₅
M49 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-t-butyl
M50 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-iso-butyl
M51 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-sec-butyl
M52 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-cyclohexyl
M53 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-t-butoxy
M54 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-isopropoxy
M55 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-CF ₃
M56 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-CH ₂ CF ₃
M57 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-OCF ₃
M58 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-Cl
M59 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-Br
M60 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-I
M61 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-n-butyl
M62 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-n-propyl
M63 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-iso-propyl
M64 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-p-C ₆ H ₄ -C ₆ H ₅

wherein “(a)” means that the carbon atom of the piperazino group to which the methyl group is attached is in the R configuration and “(b)” means that the carbon atom of the piperazino group to which the methyl group is attached is in the S configuration.

Table XIV



(XIX)

and pharmaceutically acceptable salts thereof, wherein:

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<u>Compound</u>	<u>Ar</u>	<u>R₆</u>
N1 (a) and (b)	-3-(4-chloropyridazinyl)	-t-butyl
N2 (a) and (b)	-3-(4-chloropyridazinyl)	-iso-butyl
N3 (a) and (b)	-3-(4-chloropyridazinyl)	-sec-butyl
N4 (a) and (b)	-3-(4-chloropyridazinyl)	-cyclohexyl
N5 (a) and (b)	-3-(4-chloropyridazinyl)	-t-butoxy
N6 (a) and (b)	-3-(4-chloropyridazinyl)	-isopropoxy
N7 (a) and (b)	-3-(4-chloropyridazinyl)	-CF ₃
N8 (a) and (b)	-3-(4-chloropyridazinyl)	-CH ₂ CF ₃
N9 (a) and (b)	-3-(4-chloropyridazinyl)	-OCF ₃
N10 (a) and (b)	-3-(4-chloropyridazinyl)	-Cl
N11 (a) and (b)	-3-(4-chloropyridazinyl)	-Br
N12 (a) and (b)	-3-(4-chloropyridazinyl)	-I
N13 (a) and (b)	-3-(4-chloropyridazinyl)	-n-butyl
N14 (a) and (b)	-3-(4-chloropyridazinyl)	-n-propyl
N15 (a) and (b)	-3-(4-chloropyridazinyl)	-iso-propyl

N16 (a) and (b)	-3-(4-chloropyridazinyl)	-p-C ₆ H ₄ -C ₆ H ₅
N17 (a) and (b)	-3-(4-methylpyridazinyl)	-t-butyl
N18 (a) and (b)	-3-(4-methylpyridazinyl)	-iso-butyl
N19 (a) and (b)	-3-(4-methylpyridazinyl)	-sec-butyl
N20 (a) and (b)	-3-(4-methylpyridazinyl)	-cyclohexyl
N21 (a) and (b)	-3-(4-methylpyridazinyl)	-t-butoxy
N22 (a) and (b)	-3-(4-methylpyridazinyl)	-isopropoxy
N23 (a) and (b)	-3-(4-methylpyridazinyl)	-CF ₃
N24 (a) and (b)	-3-(4-methylpyridazinyl)	-CH ₂ CF ₃
N25 (a) and (b)	-3-(4-methylpyridazinyl)	-OCF ₃
N26 (a) and (b)	-3-(4-methylpyridazinyl)	-Cl
N27 (a) and (b)	-3-(4-methylpyridazinyl)	-Br
N28 (a) and (b)	-3-(4-methylpyridazinyl)	-I
N29 (a) and (b)	-3-(4-methylpyridazinyl)	-n-butyl
N30 (a) and (b)	-3-(4-methylpyridazinyl)	-n-propyl
N31 (a) and (b)	-3-(4-methylpyridazinyl)	-iso-propyl
N32 (a) and (b)	-3-(4-methylpyridazinyl)	-p-C ₆ H ₄ -C ₆ H ₅
N33 (a) and (b)	-3-(4-fluoropyridazinyl)	-t-butyl
N34 (a) and (b)	-3-(4-fluoropyridazinyl)	-iso-butyl
N35 (a) and (b)	-3-(4-fluoropyridazinyl)	-sec-butyl
N36 (a) and (b)	-3-(4-fluoropyridazinyl)	-cyclohexyl
N37 (a) and (b)	-3-(4-fluoropyridazinyl)	-t-butoxy
N38 (a) and (b)	-3-(4-fluoropyridazinyl)	-isopropoxy
N39 (a) and (b)	-3-(4-fluoropyridazinyl)	-CF ₃
N40 (a) and (b)	-3-(4-fluoropyridazinyl)	-CH ₂ CF ₃
N41 (a) and (b)	-3-(4-fluoropyridazinyl)	-OCF ₃
N42 (a) and (b)	-3-(4-fluoropyridazinyl)	-Cl

N43 (a) and (b)	-3-(4-fluoropyridazinyl)	-Br
N44 (a) and (b)	-3-(4-fluoropyridazinyl)	-I
N45 (a) and (b)	-3-(4-fluoropyridazinyl)	-n-butyl
N46 (a) and (b)	-3-(4-fluoropyridazinyl)	-n-propyl
N47 (a) and (b)	-3-(4-fluoropyridazinyl)	-iso-propyl
N48 (a) and (b)	-3-(4-fluoropyridazinyl)	-p-C ₆ H ₄ -C ₆ H ₅
N49 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-t-butyl
N50 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-iso-butyl
N51 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-sec-butyl
N52 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-cyclohexyl
N53 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-t-butoxy
N54 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-isopropoxy
N55 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-CF ₃
N56 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-CH ₂ CF ₃
N57 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-OCF ₃
N58 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-Cl
N59 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-Br
N60 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-I
N61 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-n-butyl
N62 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-n-propyl
N63 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-iso-propyl
N64 (a) and (b)	-3-(4-methyl-6-chloropyridazinyl)	-p-C ₆ H ₄ -C ₆ H ₅

wherein “(a)” means that the carbon atom of the piperazino group to which the methyl group is attached is in the R configuration and “(b)” means that the carbon atom of the piperazino group to which the methyl group is attached is in the S configuration.

3.6 Definitions

As used herein, the terms used above having following meaning:

“(C₁-C₁₀)alkyl” means a straight chain or branched non-cyclic hydrocarbon having from 1 to 10 carbon atoms. Representative straight chain -(C₁-C₁₀)alkyls include
5 -methyl, -ethyl, -n-propyl, -n-butyl, -n-pentyl, -n-hexyl, -n-heptyl, -n-octyl, -n-nonyl and -n-decyl. Representative branched -(C₁-C₁₀)alkyls include -isopropyl, -sec-butyl, -isobutyl, -tert-butyl, -isopentyl, -neopentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1-ethylbutyl, 2-ethylbutyl, 3-ethylbutyl, 1,1-dimethylbutyl,
10 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, 1-methylhexyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 1,2-dimethylpentyl, 1,3-dimethylpentyl, 1,2-dimethylhexyl, 1,3-dimethylhexyl, 3,3-dimethylhexyl, 1,2-dimethylheptyl, 1,3-dimethylheptyl, and 3,3-dimethylheptyl.

“(C₁-C₆)alkyl” means a straight chain or branched non-cyclic hydrocarbon having from 1 to 6 carbon atoms. Representative straight chain -(C₁-C₆)alkyls include -methyl, -ethyl, -n-propyl, -n-butyl, -n-pentyl and -n-hexyl. Representative branched -(C₁-C₆)alkyls include -isopropyl, -sec-butyl, -isobutyl, -tert-butyl, -isopentyl, -neopentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl,
20 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1-ethylbutyl, 2-ethylbutyl, 3-ethylbutyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl and 3,3-dimethylbutyl.

“(C₂-C₁₀)alkenyl” means a straight chain or branched non-cyclic hydrocarbon having from 2 to 10 carbon atoms and including at least one carbon-carbon
25 double bond. Representative straight chain and branched (C₂-C₁₀)alkenyls include -vinyl, -allyl, -1-butenyl, -2-butenyl, -isobutylenyl, -1-pentenyl, -2-pentenyl, -3-methyl-1-butenyl, -2-methyl-2-butenyl, -2,3-dimethyl-2-butenyl, -1-hexenyl, -2-hexenyl, -3-hexenyl, -1-heptenyl, -2-heptenyl, -3-heptenyl, -1-octenyl, -2-octenyl, -3-octenyl, -1-nonenyl, -2-nonenyl, -3-nonenyl, -1-decenyl, -2-decenyl, -3-decenyl and the like.

“(C₂-C₆)alkenyl” means a straight chain or branched non-cyclic hydrocarbon having from 2 to 6 carbon atoms and including at least one carbon-carbon
double bond. Representative straight chain and branched (C₂-C₆)alkenyls include -vinyl, -allyl, -1-butenyl, -2-butenyl, -isobutylenyl, -1-pentenyl, -2-pentenyl, -3-methyl-1-butenyl, -2-methyl-2-butenyl, -2,3-dimethyl-2-butenyl, -1-hexenyl, 2-hexenyl, 3-hexenyl and the like.

“(C₂-C₁₀)alkynyl” means a straight chain or branched non-cyclic hydrocarbon having from 2 to 10 carbon atoms and including at least one carbon-carbon triple bond. Representative straight chain and branched (C₂-C₁₀)alkynyls include -acetylenyl, -propynyl, -1-butyne, -2-butyne, -1-pentyne, -2-pentyne, -3-methyl-1-butyne, -4-pentyne, -1-hexyne, -2-hexyne, -5-hexyne, -1-heptyne, -2-heptyne, -6-heptyne, -1-octyne, -2-octyne, -7-octyne, -1-nonyne, -2-nonyne, -8-nonyne, -1-decynyl, -2-decynyl, -9-decynyl and the like.

“(C₂-C₆)alkynyl” means a straight chain or branched non-cyclic hydrocarbon having from 2 to 6 carbon atoms and including at least one carbon-carbon triple bond. Representative straight chain and branched (C₂-C₆)alkynyls include -acetylenyl, -propynyl, -1-butyne, -2-butyne, -1-pentyne, -2-pentyne, -3-methyl-1-butyne, -4-pentyne, -1-hexyne, -2-hexyne, -5-hexyne and the like.

“(C₃-C₁₀)cycloalkyl” means a saturated cyclic hydrocarbon having from 3 to 10 carbon atoms. Representative (C₃-C₁₀)cycloalkyls are -cyclopropyl, -cyclobutyl, -cyclopentyl, -cyclohexyl, -cycloheptyl, -cyclooctyl, -cyclononyl and -cyclodecyl.

“(C₃-C₈)cycloalkyl” means a saturated cyclic hydrocarbon having from 3 to 8 carbon atoms. Representative (C₃-C₈)cycloalkyls include -cyclopropyl, -cyclobutyl, -cyclopentyl, -cyclohexyl, -cycloheptyl and -cyclooctyl.

“(C₈-C₁₄)bicycloalkyl” means a bi-cyclic hydrocarbon ring system having from 8 to 14 carbon atoms and at least one saturated cyclic alkyl ring. Representative (C₈-C₁₄)bicycloalkyls include -indanyl, -1,2,3,4-tetrahydronaphthyl, -5,6,7,8-tetrahydronaphthyl, -perhydronaphthyl and the like.

“(C₈-C₁₄)tricycloalkyl” means a tri-cyclic hydrocarbon ring system having from 8 to 14 carbon atoms and at least one saturated ring. Representative (C₈-C₁₄)tricycloalkyls include -pyrenyl, -1,2,3,4-tetrahydroanthracenyl, -perhydroanthracenyl -aceanthrenyl, -1,2,3,4-tetrahydropenanthrenyl, -5,6,7,8-tetrahydrophenanthrenyl, -perhydrophenanthrenyl and the like.

“(C₅-C₁₀)cycloalkenyl” means a cyclic non-aromatic hydrocarbon having at least one carbon-carbon double bond in the cyclic system and from 5 to 10 carbon atoms. Representative (C₅-C₁₀)cycloalkenyls include -cyclopentenyl, -cyclopentadienyl, -cyclohexenyl, -cyclohexadienyl, -cycloheptenyl, -cycloheptadienyl, -cycloheptatrienyl, -cyclooctenyl, -cyclooctadienyl, -cyclooctatrienyl, -cyclooctatetraenyl, -cyclononenyl -cyclononadienyl, -cyclodecenyl, -cyclodecadienyl and the like.

“(C₅-C₈)cycloalkenyl” means a cyclic non-aromatic hydrocarbon having at least one carbon-carbon double bond in the cyclic system and from 5 to 8 carbon atoms.

Representative (C₅-C₈)cycloalkenyls include -cyclopentenyl, -cyclopentadienyl, -cyclohexenyl, -cyclohexadienyl, -cycloheptenyl, -cycloheptadienyl, -cycloheptatrienyl, -cyclooctenyl, -cyclooctadienyl, -cyclooctatrienyl, -cyclooctatetraenyl and the like.

“(C₈-C₁₄)bicycloalkenyl” means a bi-cyclic hydrocarbon ring system having at least one carbon-carbon double bond in each ring and from 8 to 14 carbon atoms.

Representative -(C₈-C₁₄)bicycloalkenyls include -indenyl, -pentalenyl, -naphthalenyl, -azulenyl, -heptalenyl, -1,2,7,8-tetrahydronaphthalenyl and the like.

“(C₈-C₁₄)tricycloalkenyl” means a tri-cyclic hydrocarbon ring system having at least one carbon-carbon double bond in each ring and from 8 to 14 carbon atoms. Representative -(C₈-C₁₄)tricycloalkenyls include -anthracenyl, -phenanthrenyl, -phenalenyl, -acenaphthalenyl, *as*-indacenyl, *s*-indacenyl and the like.

“(3- to 7-membered)heterocycle” or “-(3- to 7-membered)heterocyclo”

means a 3- to 7-membered monocyclic heterocyclic ring which is either saturated, unsaturated non-aromatic, or aromatic. A 3-membered -(3- to 7-membered)heterocycle can contain up to 3 heteroatoms, and a 4- to 7-membered -(3- to 7-membered)heterocycle can contain up to 4 heteroatoms. Each heteroatom is independently selected from nitrogen, which can be quaternized; oxygen; and sulfur, including sulfoxide and sulfone. The -(3- to 7-membered)heterocycle can be attached via a nitrogen, sulfur, or carbon atom.

Representative -(3- to 7-membered)heterocycles include pyridyl, furyl, thiophenyl, pyrrolyl, oxazolyl, imidazolyl, thiazolyl, thiadiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, morpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, piperazinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydropyrindinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl and the like.

“(3- to 5-membered)heterocycle” or “-(3- to 5-membered)heterocyclo”

means a 3- to 5-membered monocyclic heterocyclic ring which is either saturated, unsaturated non-aromatic, or aromatic. A 3-membered -(3- to 5-membered)heterocycle can contain up to 3 heteroatoms, and a 4- to 5-membered -(3- to 5-membered)heterocycle can contain up to 4 heteroatoms. Each heteroatom is independently selected from nitrogen, which can be quaternized; oxygen; and sulfur, including sulfoxide and sulfone. The -(3- to 5-membered)heterocycle can be attached via a nitrogen, sulfur, or carbon atom.

Representative -(3- to 5-membered)heterocycles include furyl, thiophenyl, pyrrolyl,

oxazolyl, imidazolyl, thiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, triazinyl, pyrrolidinonyl, pyrrolidinyl, hydantoinyl, oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydrothiophenyl and the like.

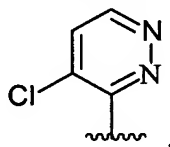
5 “-(7- to 10-membered)bicycloheterocycle” or “-(7- to 10-membered)bicycloheterocyclo” means a 7- to 10-membered bicyclic, heterocyclic ring which is either saturated, unsaturated non-aromatic, or aromatic. A -(7- to 10-membered)bicycloheterocycle contains from 1 to 4 heteroatoms independently selected from nitrogen, which can be quaternized; oxygen; and sulfur, including sulfoxide and sulfone. The -(7- to 10-membered)bicycloheterocycle can be attached via a nitrogen, sulfur,
10 or carbon atom. Representative -(7- to 10-membered)bicycloheterocycles include -quinolinyl, -isoquinolinyl, -chromonyl, -coumarinyl, -indolyl, -indolizinyl, -benzo[b]furanyl, -benzo[b]thiophenyl, -indazolyl, -purinyl, -4H-quinolizinyl, -isoquinolyl, -quinolyl, -phthalazinyl, -naphthyridinyl, -carbazolyl, - β -carbolinyl and the like.

15 “-(C₁₄)aryl” means a 14-membered aromatic carbocyclic moiety such as -anthryl or -phenanthryl.

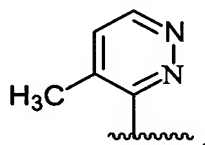
“-(5- to 10-membered)heteroaryl” means an aromatic heterocycle ring of 5 to 10 members, including both mono- and bicyclic ring systems, wherein at least one carbon atom of one or both of the rings is replaced with a heteroatom independently selected from nitrogen, oxygen and sulfur. One or both of the -(5- to 10-membered)heteroaryl’s rings
20 contain at least one carbon atom. Representative -(5- to 10-membered)heteroaryls include pyridyl, furyl, benzofuranyl, thiophenyl, benzothiophenyl, quinolinyl, pyrrolyl, indolyl, oxazolyl, benzoxazolyl, imidazolyl, benzimidazolyl, thiazolyl, benzothiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiadiazolyl, triazinyl, cinnolinyl, phthalazinyl, and quinazolinyl.

25 “-Halogen” or “-Halo” means -F, -Cl, -Br or -I.

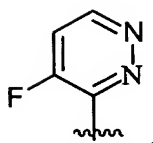
The phrase “3-(4-chloropyridazinyl)” means



The phrase “3-(4-methylpyridazinyl)” means



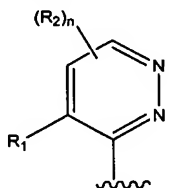
30 The phrase “3-(4-fluoropyridazinyl)” means



The phrase “-3-(4-methyl-6-chloropyridazinyl)” means

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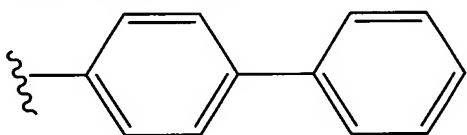
The phrase “pyridazinyl group” means



5

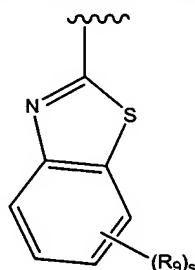
wherein R_1 , R_2 , and n are defined above for the Pyridazinylpiperazine Compounds of formula (I), (II), (III), (IV), or (V).

The phrase “-p-C₆H₄-C₆H₅” means



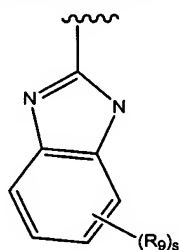
10

The phrase “benzothiazolyl group” means



wherein R_9 and s are defined above for the Pyridazinylpiperazine Compounds of formula (IV) and (V).

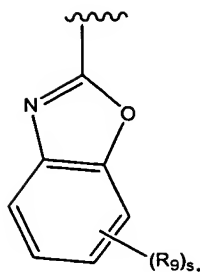
The phrase “benzoimidazolyl group” means



15

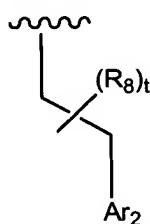
wherein R_9 and s are defined above for the Pyridazinylpiperazine Compounds of formula (IV) and (V).

The phrase “benzooxazolyl group” means



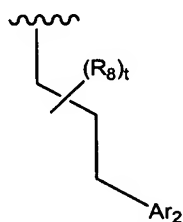
wherein R_9 and s are defined above for the Pyridazinylpiperazine Compounds of formula (IV) and (V).

5 The phrase "phenethyl group" means an ethylene group attached to a terminal Ar_2 group, wherein one or each of two hydrogens of the ethylene group can optionally be substituted with an R_8 group. A phenethyl group is depicted below:



wherein R_8 , Ar_2 , and t are defined above for the Pyridazinylpiperazine Compounds of formula (IV).

10 The phrase "phenpropyl group" an n-propylene group attached to a terminal Ar_2 group, wherein one or each of two hydrogens of the n-propylene group can optionally be substituted with an R_8 group. A phenpropyl group is depicted below



15 wherein R_8 , Ar_2 , and t are defined above for the Pyridazinylpiperazine Compounds of formula (V).

The term "animal," includes, but is not limited to, a cow, monkey, chimpanzee, baboon, horse, sheep, pig, chicken, turkey, quail, cat, dog, mouse, rat, rabbit, guinea pig and human.

20 The phrase "pharmaceutically acceptable salt," as used herein, is a salt formed from an acid and a basic nitrogen group of one of the Pyridazinylpiperazine Compounds. Illustrative salts include, but are not limited, to sulfate, citrate, acetate, oxalate, chloride, bromide, iodide, nitrate, bisulfate, phosphate, acid phosphate, isonicotinate, lactate, salicylate, acid citrate, tartrate, oleate, tannate, pantothenate, bitartrate,

ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, *p*-toluenesulfonate, and pamoate (*i.e.*, 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)) salts.

The term "pharmaceutically acceptable salt" also refers to a salt prepared from a

- 5 Pyridazinylpiperazine Compound having an acidic functional group, such as a carboxylic acid functional group, and a pharmaceutically acceptable inorganic or organic base. Suitable bases include, but are not limited to, hydroxides of alkali metals such as sodium, potassium, and lithium; hydroxides of alkaline earth metal such as calcium and magnesium; hydroxides of other metals, such as aluminum and zinc; ammonia, and organic amines, such
- 10 as unsubstituted or hydroxy-substituted mono-, di-, or trialkylamines; dicyclohexylamine; tributyl amine; pyridine; N-methyl,N-ethylamine; diethylamine; triethylamine; mono-, bis-, or tris-(2-hydroxy-lower alkyl amines), such as mono-, bis-, or tris-(2-hydroxyethyl)amine, 2-hydroxy-tert-butylamine, or tris-(hydroxymethyl)methylamine, N, N,-di-lower alkyl-N-(hydroxy lower alkyl)-amines, such as N,N,-dimethyl-N-(2-hydroxyethyl)amine, or
- 15 tri-(2-hydroxyethyl)amine; N-methyl-D-glucamine; and amino acids such as arginine, lysine, and the like.

- When a first group is "substituted with one or more" second groups, each of one or more of the first group's hydrogen atoms is replaced with a second group. In one embodiment, each carbon atom of a first group is independently substituted with one or two
- 20 second groups. In another embodiment, each carbon atom of a first group is independently substituted with only one second group.

The term "UI" means urinary incontinence.

The term "IBD" means inflammatory-bowel disease.

The term "IBS" means irritable-bowel syndrome.

- 25 The term "ALS" means amyotrophic lateral sclerosis.

The term "DMSO" means dimethyl sulfoxide.

The term "DMF" means dimethyl formamide.

The term "DCM" means dichloromethane.

The term "LDA" means lithium diisopropylamide.

- 30 The term "HMPA" means hexamethylphosphoramide.

The term "HOBT" means 1-hydroxybenzotriazolehydrate.

The term "DIC" means 1,3-diisopropylcarbodiimide.

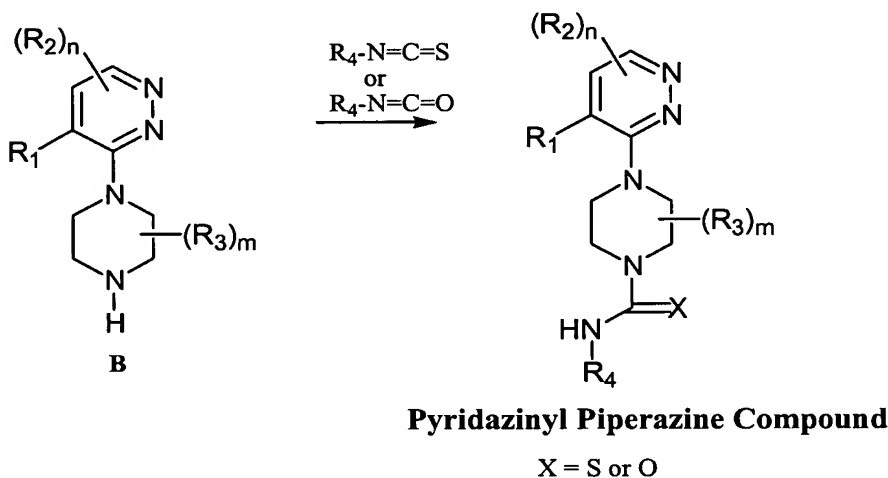
The phrase "treatment of" and "treating" includes the amelioration or cessation of a Condition or a symptom thereof.

The phrase “prevention of” and “preventing” includes the avoidance of the onset of a Condition or a symptom thereof.

3.7 METHODS FOR MAKING THE PYRIDAZINYLPIPERAZINE COMPOUNDS

The Pyridazinylpiperazine Compounds can be made using conventional organic synthesis or by the following illustrative methods shown in the schemes below.

The Pyridazinylpiperazine Compounds of Formula (I), (II), and (III) wherein A is -NH- can be obtained using conventional organic syntheses or by the following illustrative methods shown in below in Scheme A:



Scheme A

wherein R^1 - R^4 and m are as defined above.

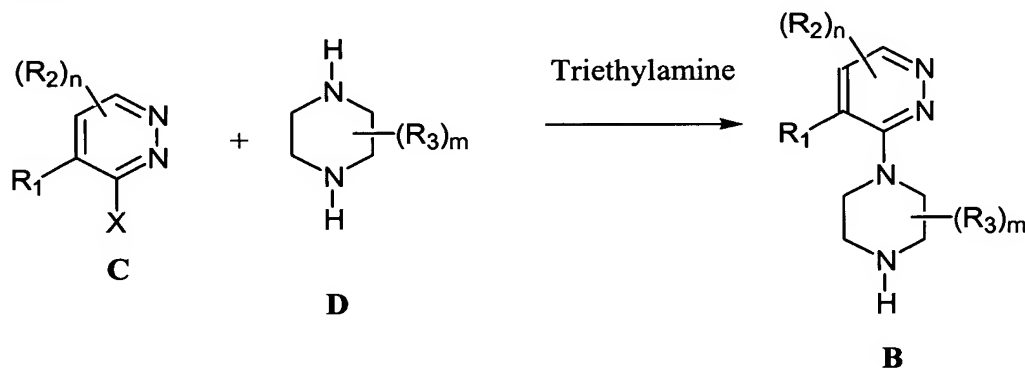
Compound **B** is reacted with an isocyanate (R_4 -N=C=O) or isothiocyanate (R_4 -N=C=S) in a suitable solvent, preferably DCM, at a suitable temperature, preferably at room temperature, to provide the Pyridazinylpiperazine Compound wherein X = O or X = S, respectively, and A is -NH-.

If the Pyridazinylpiperazine Compound is substituted with a hydroxyl group or thiol group, then the hydroxyl or thiol group of compound **B** is preferably protected with a suitable protecting group before being reacted with the isocyanate or isothiocyanate. Suitable protecting groups for hydroxyl group include, but are not limited to, methyl ether, methoxymethyl ether, methoxythiomethyl ether, 2-methoxyethoxymethyl ether, bis(2-chloroethoxy)ethyl ether, tetrahydropyranyl ether, tetrahydrothiopyranyl ether, 4-methoxytetrahydropyranyl ether, methoxytetrahydrothiopyranyl ether, tetrahydrofuranyl ether, tetrahydrothiofuranyl ether, 1-ethoxyethyl ether, 1-methyl-1-methoxyethyl ether, 2-(phenylselenyl ether), *t*-butyl ether, allyl ether, benzyl ether, *o*-nitrobenzyl ether, triphenylmethyl ether, *o*-naphthyl diphenylmethyl ether, *p*-methoxydiphenylmethyl ether, 9-

(9-phenyl-10-oxo)anthryl ether (tritylone), trimethylsilyl ether, isopropyl dimethylsilyl ether, *t*-butyl dimethylsilyl ether, *t*-butyl diphenylsilyl ether, tribenzylsilyl ether, triisopropylsilyl ether, formate ester, acetate ester, trichloroacetate ester, phenoxyacetate ester, isobutyrate ester, pivaloate ester, adamantate ester, benzoate ester, 2,4,6-trimethyl (mesitoate) ester, methyl carbonate, 2,2,2-trichlorocarbonate, allyl carbonate, *p*-nitrophenyl carbonate, benzyl carbonate, *p*-nitrobenzyl carbonate, *S*-benzylthiocarbonate, *N*-phenylcarbamate, nitrate ester, and 2,4-dinitrophenylsulfonate ester (*See, e.g.*, T.W. Greene, *Protective Groups in Organic Synthesis* 10-72 (1981)).

Suitable protecting groups for a thiol group include, but are not limited to, *S*-benzyl thioether, *S-p*-methoxybenzyl thioether, *S-p*-nitrobenzyl thioether, *S*-4-picolyl thioether, *S*-2-picolyl *N*-oxide thioether, *S*-9-anthrylmethyl thioether, *S*-diphenylmethyl thioether, *S*-di(*p*-methoxyphenyl)methyl thioether, *S*-triphenylmethyl thioether, *S*-2,4-dinitrophenyl thioether, *S-t*-butyl thioether, *S*-isobutoxymethyl hemithioacetal, *S*-2-tetrahydropyranyl hemithioacetal, *S*-acetamidomethyl aminothioacetal, *S*-cyanomethyl thioether, *S*-2-nitro-1-phenylethyl thioether, *S*-2,2-bis(carboethoxy)ethyl thioether, *S*-benzoyl derivative, *S*-(*N*-ethylcarbamate), and *S*-ethyl disulfide. *Id.* at 193-217.

The compound of formula **B** can be prepared by reacting a 3-halo-substituted pyridazine of formula **C** with a piperazine **D** in chloroform, in the presence of triethylamine at a temperature of about 50°C as shown below in Scheme B.



Scheme B

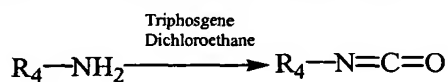
wherein X is I, Br, Cl, or F.

A representative procedure for reacting a 3-halo-pyridazine with piperazine is provided in E. J. Jacobsen et al., *J. Med. Chem.* 1145-1151 (1990).

The substituted 3-halo-pyridazines **C** are commercially available or can be prepared by methods well known to those skilled in the art.

Isocyanates $R_4-N=C=O$ are commercially available or preparable by reacting R_4NH_2 with phosgene according to well-known methods (*See, e.g.*, H. Eckert et al., *Angew.*

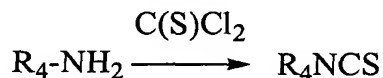
Chem. Int. Ed. Engl. **26**:894 (1987); H. Eckert, Ger. Offen. DE 3 440 141; *Chem Abstr.* **106**:4294d (1987); and L. Contarca et al., *Synthesis* 553-576 (1996)). For example an amine, R_4-NH_2 , can be reacted with triphosgene according to the Scheme C shown below.



Scheme C

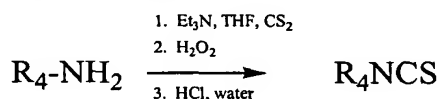
Typically, a solution of triphosgene (0.3 eq) in 1,2-dichloroethane (0.3 M) is slowly added to a stirred solution of the amine (1.0 eq.) in 1, 2-dichloroethane (0.3 M) at room temperature. The reaction mixture is then stirred at room temperature for about 10 min. and the temperature then raised to about 70° C. After stirring at about 70 °C for about 3 h, the reaction mixture is cooled to room temperature, filtered, and the filtrate concentrated to give the desired isocyanate.

Isothiocyanates, $R_4-N=C=S$, are commercially available or preparable by reacting R_4NH_2 with thiophosgene as shown below in Scheme D (See, e.g., *Tetrahedron Lett.*, **41**(37):7207-7209 (2000); *Synlett* **11**:1784-1786 (1999); *Heterocycles* **32**:2343-2355 (1991); *Org. Prep., Proced., Int.* **23**(6):729-734 (1991); *J. Heterocycle Chem.* **28**(4):1091-1097 (1991); *J. Fluorine Chem.* **41**(3):303-310 (1988); *J. Med. Chem.* **32**(6):1173-1176 and 1392-1398 (1989); and *Tetrahedron Lett.* **42**(32):5414-5416 (2001).



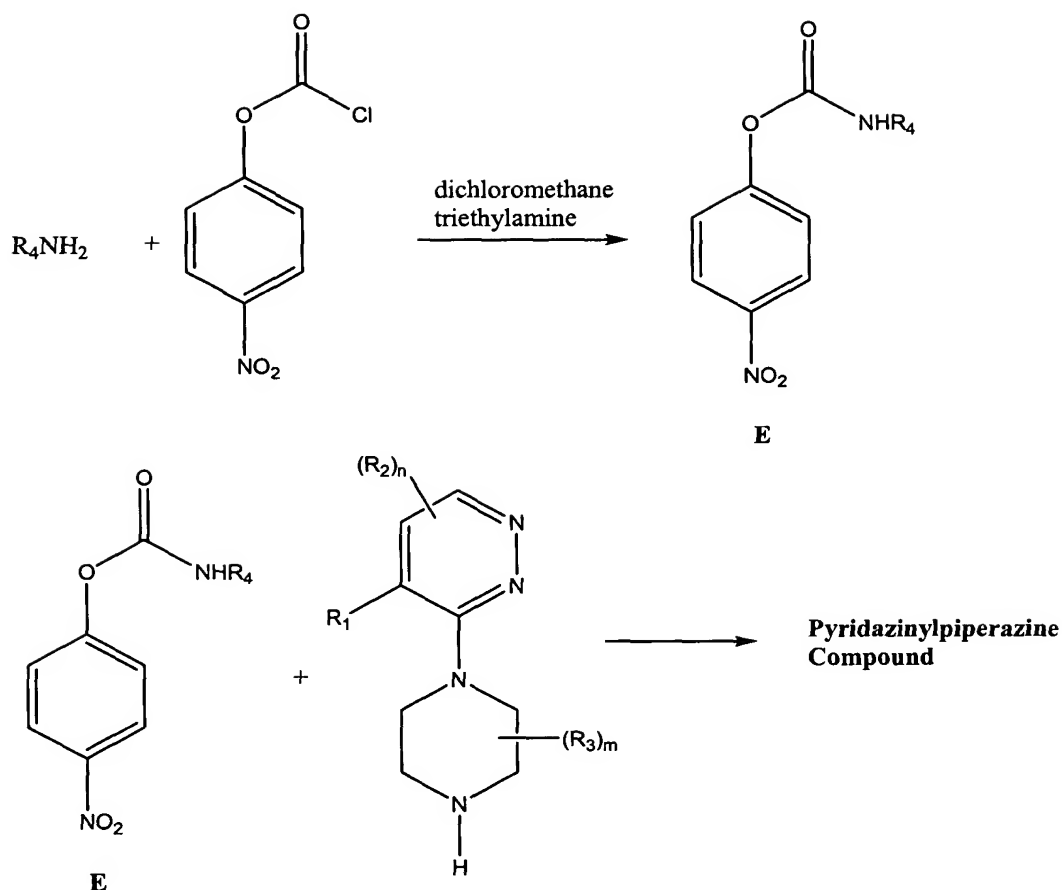
Scheme D

Alternatively, isothiocyanates $R_4-N=C=S$ can be prepared by reacting R_4NH_2 with carbon disulfide in the presence of triethylamine in tetrahydrofuran, followed by reaction with hydrogen peroxide and hydrochloric acid in water as shown below in Scheme E (See, e.g., *J. Org. Chem.*, **62** (13), 4539-4540 (1997)).

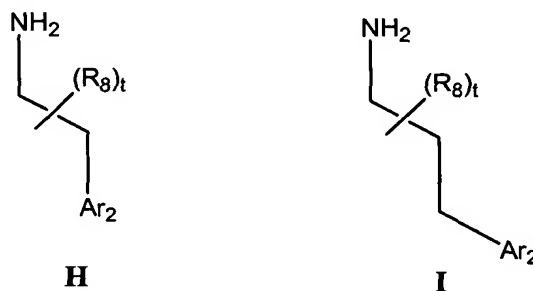


Scheme E

The Pyridazinylpiperazine Compounds of Formula (I), (II), and (III) wherein A is -NH- can also be prepared by reacting R_4NH_2 with 4-nitrophenylchloroformate (commercially available from Sigma-Aldrich, St. Louis, MO (www.sigma-aldrich.com)) to provide a carbamate, Compound E, and then reacting Compound E with Compound B as shown below in Scheme F (See, e.g., *J. Org. Chem.* **63**(23):8515-8521 (1998) and European Patent Publication No. 549 039.



- The Pyridazinylpiperazine Compounds of Formula (IV) and (V) can be prepared by a method analogous to that described in Scheme F to make the
- 5 Pyridazinylpiperazine Compounds of Formula (I), (II), and (III) wherein A is -NH-, except that an amine of formula **H** or **I**,

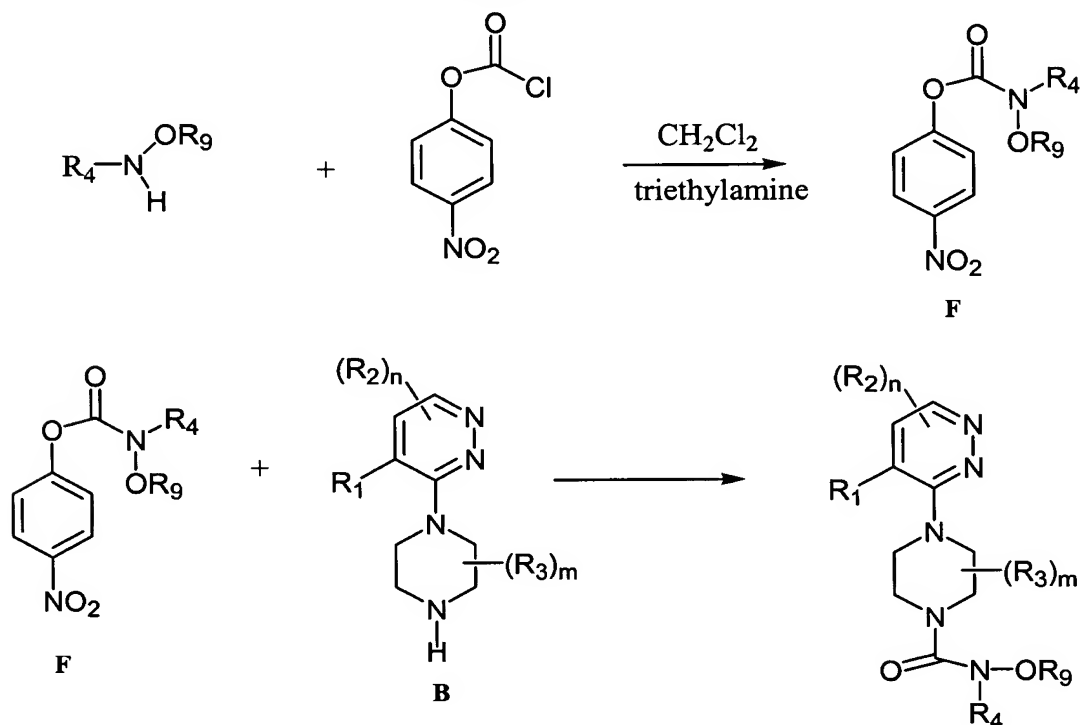


- wherein R_8 , Ar_2 , and t are defined above for the Pyridazinylpiperazine Compounds of Formula (IV) and (V), is used in place of the amine of formula R_4-NH_2 . The amines of
- 10 formula **H** and **I** are commercially available or can be made by methods well known to those skilled in the art.

The Pyridazinylpiperazine Compounds of Formula (I), (II), (III) wherein A is -N(C₁-C₆ alkyl)- can be prepared by alkylating the urea or thiourea nitrogen atom of the

Pyridazinylpiperazine Compounds of Formula (I), (II), (III) wherein A is -NH-. The Pyridazinylpiperazine Compounds of Formula (I), (II), (III) wherein A is -NH- can be alkylated using sodium hydride in an anhydrous aprotic solvent followed by reaction with a C₁-C₆ alkyl halide, such as methyl iodide. C₁-C₆ alkyl halides are commercially available or can be prepared by methods well known to those skilled in the art.

The Pyridazinylpiperazine Compounds of Formula (I) wherein A is -N(O-C₁-C₆ alkyl)- can be obtained using conventional organic syntheses or by the following illustrative method shown below in Scheme G:

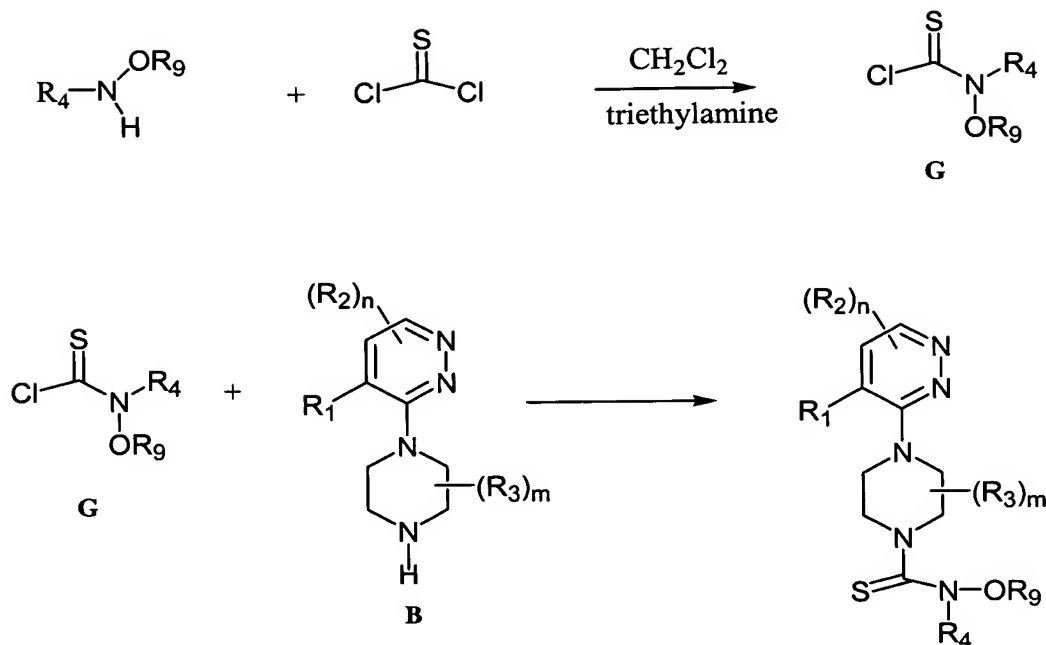


Scheme G

wherein R₉ is a C₁-C₆ alkyl and R₄ is as defined above.

A hydroxylamine ester, R₄NHOR₉, wherein R₄ and R₉ are defined above, is reacted with 4-nitrophenyl chloroformate (commercially available from Sigma-Aldrich, St. Louis, MO (www.sigma-aldrich.com)) in 1,2-dichloroethane in the presence of triethylamine to provide a carbamate, Compound F. Compound F is then reacted with Compound B to provide the Pyridazinylpiperazine Compounds of Formula (I) wherein A is -N(O-C₁-C₆ alkyl)-. Hydroxylamine esters are commercially available or can be prepared by methods well known to those skilled in the art.

The Pyridazinylpiperazine Compounds of Formula (II) wherein A is -N(O-C₁-C₆ alkyl)- can be obtained using conventional organic syntheses or by the following illustrative methods shown below in Scheme H:

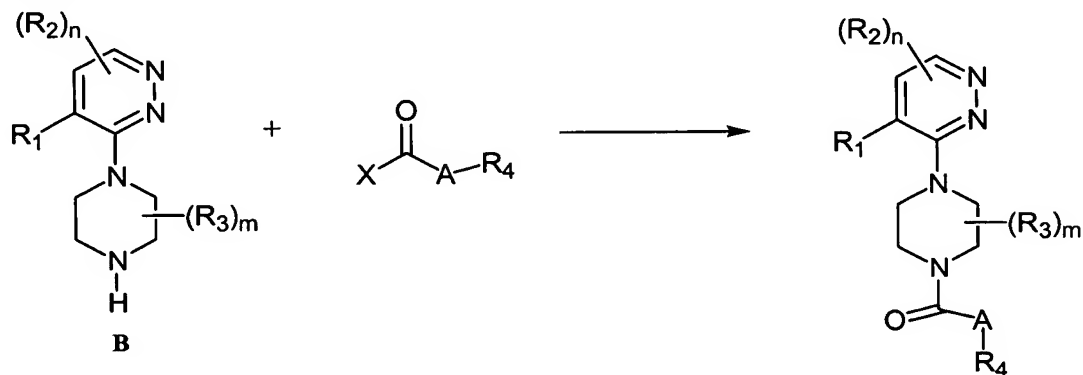


Scheme H

wherein R₉ is a C₁-C₆ alkyl and R₄ is as defined above.

- A hydroxylamine ester, R₄NHOR₉, wherein R₄ and R₉ are defined above, is
 5 reacted with thiophosgene (commercially available from Sigma-Aldrich, St. Louis, MO
 (www.sigma-aldrich.com)) in 1,2-dichloroethane in the presence of triethylamine to provide
 a Compound G. Compound G is then reacted with Compound B to provide the
 Pyridazinylpiperazine Compounds of Formula (II) wherein A is -N(O-C₁-C₆ alkyl)-.
 Hydroxylamine esters are commercially available or can be prepared by methods well
 10 known to those skilled in the art.

The Pyridazinylpiperazine Compounds of Formula (II) wherein A is -CH₂-, -
 CH₂-CH₂-, or -CH=CH- can be obtained using conventional organic syntheses or by the
 following illustrative methods shown below in the Scheme I:



Scheme I

wherein X is Cl, Br, I, or F; A is -CH₂-, -CH₂CH₂-, or -CH=CH-; and R₄ is as defined above.

Compound **B** is reacted with an acid halide of formula X-C(O)-A-R₄, wherein X, A, and R₄ are defined above, to provide the Pyridazinylpiperazine Compound of Formula (II) wherein A is -CH₂-, -CH₂CH₂-, or -CH=CH-. A representative procedure for coupling an acid chloride with an amine is provided in T.R. Herrin et al., *J. Med. Chem.* 1216-1223 (1975). Methods for preparing acid halides are well known to those skilled in the art and are described in J. March, *Advanced Organic Chemistry, Reaction Mechanisms and Structure* John Wiley & Sons, NY, pp. 437-8 (4th ed. 1992). For example, acid halides can be prepared by reacting the carboxylic acid with thionyl chloride, bromide, or iodide. An acid chloride can also be prepared by reacting a carboxylic acid with phosphorous trichloride or tribromide. An acid chloride can also be prepared by reacting the carboxylic acid with Ph₃P in carbon tetrachloride. An acid fluoride can be obtained by reacting a carboxylic acid with cyanuric fluoride.

3.8 THERAPEUTIC USES OF THE PYRIDAZINYLPYPERAZINE COMPOUNDS

In accordance with the invention, the Pyridazinylpiperazine Compounds are administered to an animal in need of treatment or prevention of a Condition.

In one embodiment, an effective amount of a Pyridazinylpiperazine Compound can be used to treat or prevent any condition treatable or preventable by inhibiting VR1. Examples of conditions that are treatable or preventable by inhibiting VR1 include, but are not limited to, pain, UI, an ulcer, IBD, and IBS.

In another embodiment, an effective amount of a Pyridazinylpiperazine Compound can be used to treat or prevent any condition treatable or preventable by inhibiting mGluR5. Examples of conditions that are treatable or preventable by inhibiting mGluR5 include, but are not limited to, pain, an addictive disorder, Parkinson's disease, parkinsonism, anxiety, a pruritic condition, and psychosis.

In another embodiment, an effective amount of a Pyridazinylpiperazine Compound can be used to treat or prevent any condition treatable or preventable by inhibiting mGluR1. Examples of conditions that are treatable or preventable by inhibiting mGluR1 include, but are not limited to, pain, UI, an addictive disorder, Parkinson's disease, parkinsonism, anxiety, epilepsy, stroke, a seizure, a pruritic condition, psychosis, a cognitive disorder, a memory deficit, restricted brain function, Huntington's chorea, ALS, dementia, retinopathy, a muscle spasm, a migraine, vomiting, dyskinesia, and depression.

The Pyridazinylpiperazine Compounds can be used to treat or prevent acute or chronic pain. Examples of pain treatable or preventable using the Pyridazinylpiperazine Compounds include, but are not limited to, cancer pain, central pain, labor pain, myocardial infarction pain, pancreatic pain, colic pain, post-operative pain, headache pain, muscle pain, pain associated with intensive care, arthritic pain, and pain associated with a periodontal disease, including gingivitis and periodontitis.

The pain to be inhibited, treated or prevented may be associated with inflammation associated with an inflammatory disease, which can arise where there is an inflammation of the body tissue, and which can be a local inflammatory response and/or a systemic inflammation. For example, the Pyridazinylpiperazine Compounds can be used to inhibit, treat, or prevent pain associated with inflammatory disease including, but not limited to: organ transplant rejection; reoxygenation injury resulting from organ transplantation (see Grupp *et al.*, *J. Mol. Cell Cardiol.* 31:297-303 (1999)) including, but not limited to, transplantation of the heart, lung, liver, or kidney; chronic inflammatory diseases of the joints, including arthritis, rheumatoid arthritis, osteoarthritis and bone diseases associated with increased bone resorption; inflammatory bowel diseases, such as ileitis, ulcerative colitis, Barrett's syndrome, and Crohn's disease; inflammatory lung diseases, such as asthma, adult respiratory distress syndrome, and chronic obstructive airway disease; inflammatory diseases of the eye, including corneal dystrophy, trachoma, onchocerciasis, uveitis, sympathetic ophthalmitis and endophthalmitis; chronic inflammatory disease of the gum, including gingivitis and periodontitis; tuberculosis; leprosy; inflammatory diseases of the kidney, including uremic complications, glomerulonephritis and nephrosis; inflammatory disease of the skin, including sclerodermatitis, psoriasis and eczema; inflammatory diseases of the central nervous system, including chronic demyelinating diseases of the nervous system, multiple sclerosis, AIDS-related neurodegeneration and Alzheimer's disease, infectious meningitis, encephalomyelitis, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis and viral or autoimmune encephalitis; autoimmune diseases, including Type I and Type II diabetes mellitus; diabetic complications, including, but not limited to, diabetic cataract, glaucoma, retinopathy, nephropathy (such as microalbuminuria and progressive diabetic nephropathy), polyneuropathy, mononeuropathies, autonomic neuropathy, gangrene of the feet, atherosclerotic coronary arterial disease, peripheral arterial disease, nonketotic hyperglycemic-hyperosmolar coma, foot ulcers, joint problems, and a skin or mucous membrane complication (such as an infection, a shin spot, a candidal infection or necrobiosis lipoidica diabetorum); immune-complex vasculitis, and systemic lupus

erythematosus (SLE); inflammatory disease of the heart, such as cardiomyopathy, ischemic heart disease hypercholesterolemia, and arteriosclerosis; as well as various other diseases that can have significant inflammatory components, including preeclampsia, chronic liver failure, brain and spinal cord trauma, and cancer. The Pyridazinylpiperazine Compounds
5 can also be used for inhibiting, treating, or preventing pain associated with inflammatory disease that can, for example, be a systemic inflammation of the body, exemplified by gram-positive or gram negative shock, hemorrhagic or anaphylactic shock, or shock induced by cancer chemotherapy in response to pro-inflammatory cytokines, *e.g.*, shock associated with pro-inflammatory cytokines. Such shock can be induced, *e.g.*, by a chemotherapeutic
10 agent that is administered as a treatment for cancer.

The Pyridazinylpiperazine Compounds can be used to treat or prevent UI. Examples of UI treatable or preventable using the Pyridazinylpiperazine Compounds include, but are not limited to, urge incontinence, stress incontinence, overflow incontinence, neurogenic incontinence, and total incontinence.

15 The Pyridazinylpiperazine Compounds can be used to treat or prevent an ulcer. Examples of ulcers treatable or preventable using the Pyridazinylpiperazine Compounds include, but are not limited to, a duodenal ulcer, a gastric ulcer, a marginal ulcer, an esophageal ulcer, or a stress ulcer.

The Pyridazinylpiperazine Compounds can be used to treat or prevent IBD,
20 including Crohn's disease and ulcerative colitis.

The Pyridazinylpiperazine Compounds can be used to treat or prevent IBS. Examples of IBS treatable or preventable using the Pyridazinylpiperazine Compounds include, but are not limited to, spastic-colon-type IBS and constipation-predominant IBS.

The Pyridazinylpiperazine Compounds can be used to treat or prevent an
25 addictive disorder, including but not limited to, an eating disorder, an impulse-control disorder, an alcohol-related disorder, a nicotine-related disorder, an amphetamine-related disorder, a cannabis-related disorder, a cocaine-related disorder, an hallucinogen-related disorder, an inhalant-related disorders, and an opioid-related disorder, all of which are further sub-classified as listed below.

30 Eating disorders include, but are not limited to, Bulimia Nervosa, Nonpurging Type; Bulimia Nervosa, Purging Type; Anorexia; and Eating Disorder not otherwise specified (NOS).

Impulse control disorders include, but are not limited to, Intermittent Explosive Disorder, Kleptomania, Pyromania, Pathological Gambling, Trichotillomania, and Impulse Control Disorder not otherwise specified (NOS).

5 Alcohol-related disorders include, but are not limited to, Alcohol-Induced Psychotic Disorder with delusions, Alcohol Abuse, Alcohol Intoxication, Alcohol Withdrawal, Alcohol Intoxication Delirium, Alcohol Withdrawal Delirium, Alcohol-Induced Persisting Dementia, Alcohol-Induced Persisting Amnestic Disorder, Alcohol Dependence, Alcohol-Induced Psychotic Disorder with hallucinations, Alcohol-Induced Mood Disorder, Alcohol-Induced Anxiety Disorder, Alcohol-Induced Sexual Dysfunction, Alcohol-Induced Sleep Disorder, Alcohol-Related Disorder not otherwise specified (NOS), Alcohol Intoxication, and Alcohol Withdrawal.

Nicotine-related disorders include, but are not limited to, Nicotine Dependence, Nicotine Withdrawal, and Nicotine-Related Disorder not otherwise specified (NOS).

15 Amphetamine-related disorders include, but are not limited to, Amphetamine Dependence, Amphetamine Abuse, Amphetamine Intoxication, Amphetamine Withdrawal, Amphetamine Intoxication Delirium, Amphetamine-Induced Psychotic Disorder with delusions, Amphetamine-Induced Psychotic Disorders with hallucinations, Amphetamine-Induced Mood Disorder, Amphetamine-Induced Anxiety Disorder, 20 Amphetamine-Induced Sexual Dysfunction, Amphetamine-Induced Sleep Disorder, Amphetamine Related Disorder not otherwise specified (NOS), Amphetamine Intoxication, and Amphetamine Withdrawal.

Cannabis-related disorders include, but are not limited to, Cannabis Dependence, Cannabis Abuse, Cannabis Intoxication, Cannabis Intoxication Delirium, 25 Cannabis-Induced Psychotic Disorder with delusions, Cannabis-Induced Psychotic Disorder with hallucinations, Cannabis-Induced Anxiety Disorder, Cannabis Related Disorder not otherwise specified (NOS), and Cannabis Intoxication.

Cocaine-related disorders include, but are not limited to, Cocaine Dependence, Cocaine Abuse, Cocaine Intoxication, Cocaine Withdrawal, Cocaine 30 Intoxication Delirium, Cocaine-Induced Psychotic Disorder with delusions, Cocaine-Induced Psychotic Disorders with hallucinations, Cocaine-Induced Mood Disorder, Cocaine-Induced Anxiety Disorder, Cocaine-Induced Sexual Dysfunction, Cocaine-Induced Sleep Disorder, Cocaine Related Disorder not otherwise specified (NOS), Cocaine Intoxication, and Cocaine Withdrawal.

Hallucinogen-related disorders include, but are not limited to, Hallucinogen Dependence, Hallucinogen Abuse, Hallucinogen Intoxication, Hallucinogen Withdrawal, Hallucinogen Intoxication Delirium, Hallucinogen-Induced Psychotic Disorder with delusions, Hallucinogen-Induced Psychotic Disorders with hallucinations,

- 5 Hallucinogen-Induced Mood Disorder, Hallucinogen-Induced Anxiety Disorder, Hallucinogen-Induced Sexual Dysfunction, Hallucinogen-Induced Sleep Disorder, Hallucinogen Related Disorder not otherwise specified (NOS), Hallucinogen Intoxication, and Hallucinogen Persisting Perception Disorder (Flashbacks).

- Inhalant-related disorders include, but are not limited to, Inhalant Dependence, Inhalant Abuse, Inhalant Intoxication, Inhalant Intoxication Delirium, Inhalant-Induced Psychotic Disorder with delusions, Inhalant-Induced Psychotic Disorder with hallucinations, Inhalant-Induced Anxiety Disorder, Inhalant Related Disorder not otherwise specified (NOS), and Inhalant Intoxication.
- 10

- Opioid-related disorders include, but are not limited to, Opioid Dependence, Opioid Abuse, Opioid Intoxication, Opioid Intoxication Delirium, Opioid-Induced Psychotic Disorder with delusions, Opioid-Induced Psychotic Disorder with hallucinations, Opioid-Induced Anxiety Disorder, Opioid Related Disorder not otherwise specified (NOS), Opioid Intoxication, and Opioid Withdrawal.
- 15

- The Pyridazinylpiperazine Compounds can be used to treat or prevent Parkinson's disease and parkinsonism and the symptoms associated with Parkinson's disease and parkinsonism, including but not limited to, bradykinesia, muscular rigidity, resting tremor, and impairment of postural balance.
- 20

- The Pyridazinylpiperazine Compounds can be used to treat or prevent generalized anxiety or severe anxiety and the symptoms associated with anxiety, including but not limited to, restlessness; tension; tachycardia; dyspnea; depression, including chronic "neurotic" depression; panic disorder; agoraphobia and other specific phobias; eating disorders; and personality disorders.
- 25

- The Pyridazinylpiperazine Compounds can be used to treat or prevent epilepsy, including but not limited to, partial epilepsy, generalized epilepsy, and the symptoms associated with epilepsy, including but not limited to, simple partial seizures, jacksonian seizures, complex partial (psychomotor) seizures, convulsive seizures (grand mal or tonic-clonic seizures), petit mal (absence) seizures, and status epilepticus.
- 30

The Pyridazinylpiperazine Compounds can be used to treat or prevent a stroke, including but not limited to, an ischemic stroke and a hemorrhagic stroke.

5 The Pyridazinylpiperazine Compounds can be used to treat or prevent a seizure, including but not limited to, infantile spasms, febrile seizures, and epileptic seizures.

10 The Pyridazinylpiperazine Compounds can be used to treat or prevent a pruritic condition, including but not limited to, pruritus caused by dry skin, scabies, dermatitis, herpetiformis, atopic dermatitis, *pruritus vulvae et ani*, miliaria, insect bites, pediculosis, contact dermatitis, drug reactions, urticaria, urticarial eruptions of pregnancy, psoriasis, lichen planus, lichen simplex chronicus, exfoliative dermatitis, folliculitis, bullous pemphigoid, or fiberglass dermatitis.

15 The Pyridazinylpiperazine Compounds can be used to treat or prevent psychosis, including but not limited to, schizophrenia, including paranoid schizophrenia, hebephrenic or disorganized schizophrenia, catatonic schizophrenia, undifferentiated schizophrenia, negative or deficit subtype schizophrenia, and non-deficit schizophrenia; a delusional disorder, including erotomanic subtype delusional disorder, grandiose subtype delusional disorder, jealous subtype delusional disorder, persecutory subtype delusional disorder, and somatic subtype delusional disorder; and brief psychosis.

20 The Pyridazinylpiperazine Compounds can be used to treat or prevent a cognitive disorder, including but not limited to, delirium and dementia such as multi-infarct dementia, dementia pugilistica, dementia caused by AIDS, and dementia caused by Alzheimer's disease.

25 The Pyridazinylpiperazine Compounds can be used to treat or prevent a memory deficiency, including but not limited to, dissociative amnesia and dissociative fugue.

The Pyridazinylpiperazine Compounds can be used to treat or prevent restricted brain function, including but not limited to, that caused by surgery or an organ transplant, restricted blood supply to the brain, a spinal cord injury, a head injury, hypoxia, cardiac arrest, or hypoglycemia.

30 The Pyridazinylpiperazine Compounds can be used to treat or prevent Huntington's chorea.

The Pyridazinylpiperazine Compounds can be used to treat or prevent ALS.

The Pyridazinylpiperazine Compounds can be used to treat or prevent retinopathy, including but not limited to, arteriosclerotic retinopathy, diabetic arteriosclerotic retinopathy, hypertensive retinopathy, non-proliferative retinopathy, and proliferative retinopathy.

5 The Pyridazinylpiperazine Compounds can be used to treat or prevent a muscle spasm.

The Pyridazinylpiperazine Compounds can be used to treat or prevent a migraine.

10 The Pyridazinylpiperazine Compounds can be used to treat, inhibit, or prevent vomiting, including but not limited to, nausea vomiting, dry vomiting (retching), and regurgitation.

The Pyridazinylpiperazine Compounds can be used to treat or prevent dyskinesia, including but not limited to, tardive dyskinesia and biliary dyskinesia.

15 The Pyridazinylpiperazine Compounds can be used to treat or prevent depression, including but not limited to, major depression and bipolar disorder.

Applicants believe that the Pyridazinylpiperazine Compounds are antagonists for VR1.

20 The invention also relates to methods for inhibiting VR1 function in a cell comprising contacting a cell capable of expressing VR1 with an effective amount of a Pyridazinylpiperazine Compound. This method can be used *in vitro*, for example, as an assay to select cells that express VR1 and, accordingly, are useful as part of an assay to select compounds useful for treating or preventing pain, UI, an ulcer, IBD, or IBS. The method is also useful for inhibiting VR1 function in a cell *in vivo*, in an animal, a human in one embodiment, by contacting a cell, in an animal, with an effective amount of a
25 Pyridazinylpiperazine Compound. In one embodiment, the method is useful for treating or preventing pain in an animal. In another embodiment, the method is useful for treating or preventing UI in an animal. In another embodiment, the method is useful for treating or preventing an ulcer in an animal. In another embodiment, the method is useful for treating or preventing IBD in an animal. In another embodiment, the method is useful for treating or
30 preventing IBS in an animal.

Examples of tissue comprising cells capable of expressing VR1 include, but are not limited to, neuronal, brain, kidney, urothelium, and bladder tissue. Methods for assaying cells that express VR1 are well known in the art.

Applicants believe that the Pyridazinylpiperazine Compounds are antagonists for mGluR5.

The invention also relates to methods for inhibiting mGluR5 function in a cell comprising contacting a cell capable of expressing mGluR5 with an amount of a
5 Pyridazinylpiperazine Compound effective to inhibit mGluR5 function in the cell. This method can be used *in vitro*, for example, as an assay to select cells that express mGluR5 and, accordingly, are useful as part of an assay to select compounds useful for treating or preventing pain, an addictive disorder, Parkinson's disease, parkinsonism, anxiety, a pruritic condition, or psychosis. The method is also useful for inhibiting mGluR5 function in a cell
10 *in vivo*, in an animal, a human in one embodiment, by contacting a cell, in an animal, with an amount of a Pyridazinylpiperazine Compound effective to inhibit mGluR5 function in the cell. In one embodiment, the method is useful for treating or preventing pain in an animal in need thereof. In another embodiment, the method is useful for treating or preventing an addictive disorder in an animal in need thereof. In another embodiment, the
15 method is useful for treating or preventing Parkinson's disease in an animal in need thereof. In another embodiment, the method is useful for treating or preventing parkinsonism in an animal in need thereof. In another embodiment, the method is useful for treating or preventing anxiety in an animal in need thereof. In another embodiment, the method is useful for treating or preventing a pruritic condition in an animal in need thereof. In another
20 embodiment, the method is useful for treating or preventing psychosis in an animal in need thereof.

Examples of cells capable of expressing mGluR5 are neuronal and glial cells of the central nervous system, particularly the brain, especially in the nucleus accumbens. Methods for assaying cells that express mGluR5 are well known in the art.

25 Applicants believe that the Pyridazinylpiperazine Compounds are antagonists for mGluR1.

The invention also relates to methods for inhibiting mGluR1 function in a cell comprising contacting a cell capable of expressing mGluR1 with an amount of a
30 Pyridazinylpiperazine Compound effective to inhibit mGluR1 function in the cell. This method can be used *in vitro*, for example, as an assay to select cells that express mGluR1 and, accordingly, are useful as part of an assay to select compounds useful for treating or preventing pain, UI, an addictive disorder, Parkinson's disease, parkinsonism, anxiety, epilepsy, stroke, a seizure, a pruritic condition, psychosis, a cognitive disorder, a memory deficit, restricted brain function, Huntington's chorea, ALS, dementia, retinopathy, a muscle

spasm, a migraine, vomiting, dyskinesia, or depression. The method is also useful for inhibiting mGluR1 function in a cell *in vivo*, in an animal, a human in one embodiment, by contacting a cell, in an animal, with an amount of a Pyridazinylpiperazine Compound effective to inhibit mGluR1 function in the cell. In one embodiment, the method is useful for treating or preventing pain in an animal in need thereof. In another embodiment, the method is useful for treating or preventing UI in an animal in need thereof. In another embodiment, the method is useful for treating or preventing an addictive disorder in an animal in need thereof. In another embodiment, the method is useful for treating or preventing Parkinson's disease in an animal in need thereof. In another embodiment, the method is useful for treating or preventing parkinsonism in an animal in need thereof. In another embodiment, the method is useful for treating or preventing anxiety in an animal in need thereof. In another embodiment, the method is useful for treating or preventing epilepsy in an animal in need thereof. In another embodiment, the method is useful for treating or preventing stroke in an animal in need thereof. In another embodiment, the method is useful for treating or preventing a seizure in an animal in need thereof. In another embodiment, the method is useful for treating or preventing a pruritic condition in an animal in need thereof. In another embodiment, the method is useful for treating or preventing psychosis in an animal in need thereof. In another embodiment, the method is useful for treating or preventing a cognitive disorder in an animal in need thereof. In another embodiment, the method is useful for treating or preventing a memory deficit in an animal in need thereof. In another embodiment, the method is useful for treating or preventing restricted brain function in an animal in need thereof. In another embodiment, the method is useful for treating or preventing Huntington's chorea in an animal in need thereof. In another embodiment, the method is useful for treating or preventing ALS in an animal in need thereof. In another embodiment, the method is useful for treating or preventing dementia in an animal in need thereof. In another embodiment, the method is useful for treating or preventing retinopathy in an animal in need thereof. In another embodiment, the method is useful for treating or preventing a muscle spasm in an animal in need thereof. In another embodiment, the method is useful for treating or preventing a migraine in an animal in need thereof. In another embodiment, the method is useful for treating or preventing vomiting in an animal in need thereof. In another embodiment, the method is useful for treating or preventing dyskinesia in an animal in need thereof. In another embodiment, the method is useful for treating or preventing depression in an animal in need thereof.

Examples of cells capable of expressing mGluR1 include, but are not limited to, cerebellar Purkinje neuron cells, Purkinje cell bodies (punctate), cells of spine(s) of the

cerebellum; neurons and neurophil cells of olfactory-bulb glomeruli; cells of the superficial layer of the cerebral cortex; hippocampus cells; thalamus cells; superior colliculus cells; and spinal trigeminal nucleus cells. Methods for assaying cells that express mGluR1 are well known in the art.

5 **3.8.1 THERAPEUTIC/PROPHYLACTIC ADMINISTRATION
AND COMPOSITIONS OF THE INVENTION**

Due to their activity, the Pyridazinylpiperazine Compounds are advantageously useful in veterinary and human medicine. As described above, the Pyridazinylpiperazine Compounds are useful for treating or preventing a condition in an
10 animal in need thereof.

When administered to an animal, the Pyridazinylpiperazine Compounds are administered as a component of a composition that comprises a pharmaceutically acceptable carrier or excipient. The present compositions, which comprise a Pyridazinylpiperazine Compound, can be administered orally. The Pyridazinylpiperazine Compounds of the
15 invention can also be administered by any other convenient route, for example, by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (*e.g.*, oral, rectal, and intestinal mucosa, *etc.*) and can be administered together with another biologically active agent. Administration can be systemic or local. Various delivery systems are known, *e.g.*, encapsulation in liposomes, microparticles, microcapsules, or
20 capsules and can be used to administer the Pyridazinylpiperazine Compound.

Methods of administration include, but are not limited to, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, oral, sublingual, intracerebral, intravaginal, transdermal, rectal, by inhalation, or topical, particularly to the ears, nose, eyes, or skin. The mode of administration is left to the
25 discretion of the practitioner. In most instances, administration will result in the release of the Pyridazinylpiperazine Compounds into the bloodstream.

In specific embodiments, it can be desirable to administer the Pyridazinylpiperazine Compounds locally. This can be achieved, for example, and not by way of limitation, by local infusion during surgery, topical application, *e.g.*, in conjunction
30 with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository or enema, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers.

In certain embodiments, it can be desirable to introduce the Pyridazinylpiperazine Compounds into the central nervous system or gastrointestinal tract by any suitable route, including intraventricular, intrathecal, and epidural injection, and enema. Intraventricular injection can be facilitated by an intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir.

Pulmonary administration can also be employed, *e.g.*, by use of an inhaler or nebulizer, and formulation with an aerosolizing agent, or via perfusion in a fluorocarbon or synthetic pulmonary surfactant. In certain embodiments, the Pyridazinylpiperazine Compounds can be formulated as a suppository, with traditional binders and excipients such as triglycerides.

In another embodiment, the Pyridazinylpiperazine Compounds can be delivered in a vesicle, in particular a liposome (*see* Langer, *Science* 249:1527-1533 (1990) and Treat *et al.*, *Liposomes in the Therapy of Infectious Disease and Cancer* 317-327 and 353-365 (1989)).

In yet another embodiment, the Pyridazinylpiperazine Compounds can be delivered in a controlled-release system or sustained-release system (*see, e.g.*, Goodson, in *Medical Applications of Controlled Release*, *supra*, vol. 2, pp. 115-138 (1984)). Other controlled- or sustained-release systems discussed in the review by Langer, *Science* 249:1527-1533 (1990) can be used. In one embodiment, a pump can be used (Langer, *Science* 249:1527-1533 (1990); Sefton, *CRC Crit. Ref. Biomed. Eng.* 14:201 (1987); Buchwald *et al.*, *Surgery* 88:507 (1980); and Saudek *et al.*, *N. Engl. J. Med.* 321:574 (1989)). In another embodiment, polymeric materials can be used (*see Medical Applications of Controlled Release* (Langer and Wise eds., 1974); *Controlled Drug Bioavailability, Drug Product Design and Performance* (Smolen and Ball eds., 1984); Ranger and Peppas, *J. Macromol. Sci. Rev. Macromol. Chem.* 23:61 (1983); Levy *et al.*, *Science* 228:190 (1985); During *et al.*, *Ann. Neurol.* 25:351 (1989); and Howard *et al.*, *J. Neurosurg.* 71:105 (1989)). In yet another embodiment, a controlled- or sustained-release system can be placed in proximity of a target of the Pyridazinylpiperazine Compounds, *e.g.*, the spinal column, brain, or gastrointestinal tract, thus requiring only a fraction of the systemic dose.

The present compositions can optionally comprise a suitable amount of a pharmaceutically acceptable excipient so as to provide the form for proper administration to the animal.

Such pharmaceutical excipients can be liquids, such as water and oils, including those of petroleum, animal, vegetable, or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. The pharmaceutical excipients can be saline, gum acacia, gelatin, starch paste, talc, keratin, colloidal silica, urea and the like. In addition, auxiliary, stabilizing, thickening, lubricating, and coloring agents can be used. In one embodiment, the pharmaceutically acceptable excipients are sterile when administered to an animal. Water is a particularly useful excipient when the Pyridazinylpiperazine Compound is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid excipients, particularly for injectable solutions. Suitable pharmaceutical excipients also include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The present compositions, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents.

The present compositions can take the form of solutions, suspensions, emulsion, tablets, pills, pellets, capsules, capsules containing liquids, powders, sustained-release formulations, suppositories, emulsions, aerosols, sprays, suspensions, or any other form suitable for use. In one embodiment, the composition is in the form of a capsule (see *e.g.*, U.S. Patent No. 5,698,155). Other examples of suitable pharmaceutical excipients are described in *Remington's Pharmaceutical Sciences* 1447-1676 (Alfonso R. Gennaro ed., 19th ed. 1995), incorporated herein by reference.

In one embodiment, the Pyridazinylpiperazine Compounds are formulated in accordance with routine procedures as a composition adapted for oral administration to human beings. Compositions for oral delivery can be in the form of tablets, lozenges, aqueous or oily suspensions, granules, powders, emulsions, capsules, syrups, or elixirs, for example. Orally administered compositions can contain one or more agents, for example, sweetening agents such as fructose, aspartame or saccharin; flavoring agents such as peppermint, oil of wintergreen, or cherry; coloring agents; and preserving agents, to provide a pharmaceutically palatable preparation. Moreover, where in tablet or pill form, the compositions can be coated to delay disintegration and absorption in the gastrointestinal tract thereby providing a sustained action over an extended period of time. Selectively permeable membranes surrounding an osmotically active driving compound are also suitable for orally administered compositions. In these latter platforms, fluid from the environment surrounding the capsule is imbibed by the driving compound, which swells to displace the agent or agent composition through an aperture. These delivery platforms can

provide an essentially zero order delivery profile as opposed to the spiked profiles of immediate release formulations. A time-delay material such as glycerol monostearate or glycerol stearate can also be used. Oral compositions can include standard excipients such as mannitol, lactose, starch, magnesium stearate, sodium saccharin, cellulose, and
5 magnesium carbonate. In one embodiment, the excipients are of pharmaceutical grade.

In another embodiment, the Pyridazinylpiperazine Compounds can be formulated for intravenous administration. Typically, compositions for intravenous administration comprise sterile isotonic aqueous buffer. Where necessary, the compositions can also include a solubilizing agent. Compositions for intravenous administration can
10 optionally include a local anesthetic such as lidocaine to lessen pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampule or sachette indicating the quantity of active agent. Where the Pyridazinylpiperazine Compounds are to be administered by infusion,
15 they can be dispensed, for example, with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the Pyridazinylpiperazine Compounds are administered by injection, an ampule of sterile water for injection or saline can be provided so that the ingredients can be mixed prior to administration.

The Pyridazinylpiperazine Compounds can be administered by controlled-
20 release or sustained-release means or by delivery devices that are well known to those of ordinary skill in the art. Examples include, but are not limited to, those described in U.S. Patent Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; 4,008,719; 5,674,533; 5,059,595; 5,591,767; 5,120,548; 5,073,543; 5,639,476; 5,354,556; and 5,733,566, each of which is incorporated herein by reference. Such dosage forms can be used to provide controlled- or
25 sustained-release of one or more active ingredients using, for example, hydropropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, microspheres, or a combination thereof to provide the desired release profile in varying proportions. Suitable controlled- or sustained-release formulations known to those of ordinary skill in the art, including those described herein,
30 can be readily selected for use with the active ingredients of the invention. The invention thus encompasses single unit dosage forms suitable for oral administration such as, but not limited to, tablets, capsules, gelcaps, and caplets that are adapted for controlled- or sustained-release.

Controlled- or sustained-release pharmaceutical compositions can have a common goal of improving drug therapy over that achieved by their non-controlled or non-sustained counterparts. In one embodiment, a controlled- or sustained-release composition comprises a minimal amount of a Pyridazinylpiperazine Compound to cure or control the condition in a minimum amount of time. Advantages of controlled- or sustained-release compositions include extended activity of the drug, reduced dosage frequency, and increased patient compliance. In addition, controlled- or sustained-release compositions can favorably affect the time of onset of action or other characteristics, such as blood levels of the Pyridazinylpiperazine Compound, and can thus reduce the occurrence of adverse side effects.

Controlled- or sustained-release compositions can initially release an amount of a Pyridazinylpiperazine Compound that promptly produces the desired therapeutic or prophylactic effect, and gradually and continually release other amounts of the Pyridazinylpiperazine Compound to maintain this level of therapeutic or prophylactic effect over an extended period of time. To maintain a constant level of the Pyridazinylpiperazine Compound in the body, the Pyridazinylpiperazine Compound can be released from the dosage form at a rate that will replace the amount of Pyridazinylpiperazine Compound being metabolized and excreted from the body. Controlled- or sustained-release of an active ingredient can be stimulated by various conditions, including but not limited to, changes in pH, changes in temperature, concentration or availability of enzymes, concentration or availability of water, or other physiological conditions or compounds.

The amount of the Pyridazinylpiperazine Compound that is effective in the treatment or prevention of a Condition can be determined by standard clinical techniques. In addition, *in vitro* or *in vivo* assays can optionally be employed to help identify optimal dosage ranges. The precise dose to be employed will also depend on the route of administration, and the seriousness of the Condition being treated and should be decided according to the judgment of the practitioner and each patient's circumstances in view of, *e.g.*, published clinical studies. Suitable effective dosage amounts, however, range from about 10 micrograms to about 2500 milligrams about every 4 h, although they are typically about 100 mg or less. In one embodiment, the effective dosage amount ranges from about 0.01 milligrams to about 100 milligrams of a Pyridazinylpiperazine Compound about every 4 h, in another embodiment, about 0.020 milligrams to about 50 milligrams about every 4 h, and in another embodiment, about 0.025 milligrams to about 20 milligrams about every 4 h. The effective dosage amounts described herein refer to total amounts administered; that is,

if more than one Pyridazinylpiperazine Compound is administered, the effective dosage amounts correspond to the total amount administered.

Where a cell capable of expressing VR1, mGluR5, or mGluR1 is contacted with a Pyridazinylpiperazine Compound *in vitro*, the amount effective for inhibiting the receptor function in a cell will typically range from about 0.01 $\mu\text{g/L}$ to about 5 mg/L, in one embodiment, from about 0.01 $\mu\text{g/L}$ to about 2.5 mg/L, in another embodiment, from about 0.01 $\mu\text{g/L}$ to about 0.5 mg/L, and in another embodiment, from about 0.01 $\mu\text{g/L}$ to about 0.25 mg/L of a solution or suspension of a pharmaceutically acceptable carrier or excipient. In one embodiment, the volume of solution or suspension is from about 1 μL to about 1 mL. In another embodiment, the volume of solution or suspension is about 200 μL .

Where a cell capable of expressing VR1, mGluR5, or mGluR1 is contacted with a Pyridazinylpiperazine Compound *in vivo*, the amount effective for inhibiting the receptor function in a cell will typically range from about 0.01 mg to about 100 mg/kg of body weight per day, in one embodiment, from about 0.1 mg to about 50 mg/kg body weight per day, and in another embodiment, from about 1 mg to about 20 mg/kg of body weight per day.

The Pyridazinylpiperazine Compounds can be assayed *in vitro* or *in vivo* for the desired therapeutic or prophylactic activity prior to use in humans. Animal model systems can be used to demonstrate safety and efficacy.

The present methods for treating or preventing a Condition in an animal in need thereof can further comprise administering to the animal being administered a Pyridazinylpiperazine Compound another therapeutic agent. In one embodiment, the other therapeutic agent is administered in an effective amount.

The present methods for inhibiting VR1 function in a cell capable of expressing VR1 can further comprise contacting the cell with an effective amount of another therapeutic agent.

The present methods for inhibiting mGluR5 function in a cell capable of expressing mGluR5 can further comprise contacting the cell with an effective amount of another therapeutic agent.

The present methods for inhibiting mGluR1 function in a cell capable of expressing mGluR1 can further comprise contacting the cell with an effective amount of another therapeutic agent.

The other therapeutic agent includes, but is not limited to, an opioid agonist, a non-opioid analgesic, a non-steroidal anti-inflammatory agent, an antimigraine agent, a Cox-II inhibitor, an antiemetic, a β -adrenergic blocker, an anticonvulsant, an antidepressant, a Ca²⁺-channel blocker, an anticancer agent, an agent for treating or preventing UI, an agent for treating or preventing an ulcer, an agent for treating or preventing IBD, an agent for treating or preventing IBS, an agent for treating addictive disorder, an agent for treating Parkinson's disease and parkinsonism, an agent for treating anxiety, an agent for treating epilepsy, an agent for treating a stroke, an agent for treating a seizure, an agent for treating a pruritic condition, an agent for treating psychosis, an agent for treating Huntington's chorea, an agent for treating ALS, an agent for treating a cognitive disorder, an agent for treating a migraine, an agent for treating vomiting, an agent for treating dyskinesia, or an agent for treating depression, and mixtures thereof.

Effective amounts of the other therapeutic agents are well known to those skilled in the art. However, it is well within the skilled artisan's purview to determine the other therapeutic agent's optimal effective-amount range. In one embodiment of the invention, where another therapeutic agent is administered to an animal, the effective amount of the Pyridazinylpiperazine Compound is less than its effective amount would be where the other therapeutic agent is not administered. In this case, without being bound by theory, it is believed that the Pyridazinylpiperazine Compounds and the other therapeutic agent act synergistically to treat or prevent a Condition.

Examples of useful opioid agonists include, but are not limited to, alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, desomorphine, dextromoramide, dezocine, diampromide, diamorphine, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene fentanyl, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levorphanol, levophenacymorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, nalbuphine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, proheptazine, promedol, properidine, propiram, propoxyphene, sufentanil, tilidine, tramadol, pharmaceutically acceptable salts thereof, and mixtures thereof.

In certain embodiments, the opioid agonist is selected from codeine, hydromorphone, hydrocodone, oxycodone, dihydrocodeine, dihydromorphone, morphine, tramadol, oxymorphone, pharmaceutically acceptable salts thereof, and mixtures thereof.

Examples of useful non-opioid analgesics include non-steroidal anti-inflammatory agents, such as aspirin, ibuprofen, diclofenac, naproxen, benoxaprofen, flurbiprofen, fenoprofen, flubufen, ketoprofen, indoprofen, piroprofen, carprofen, oxaprozin, pramoprofen, muprofen, trioxaprofen, suprofen, aminoprofen, tiaprofenic acid, fluprofen, bucloxic acid, indomethacin, sulindac, tolmetin, zomepirac, tiopinac, zidometacin, acemetacin, fentiazac, clidanac, oxpinac, mefenamic acid, meclofenamic acid, flufenamic acid, niflumic acid, tolfenamic acid, diflurisal, flufenisal, piroxicam, sudoxicam, isoxicam, and pharmaceutically acceptable salts thereof, and mixtures thereof. Other suitable non-opioid analgesics include the following, non-limiting, chemical classes of analgesic, antipyretic, nonsteroidal anti-inflammatory drugs: salicylic acid derivatives, including aspirin, sodium salicylate, choline magnesium trisalicylate, salsalate, diflunisal, salicylsalicylic acid, sulfasalazine, and olsalazin; para-aminophenol derivatives including acetaminophen and phenacetin; indole and indene acetic acids, including indomethacin, sulindac, and etodolac; heteroaryl acetic acids, including tolmetin, diclofenac, and ketorolac; anthranilic acids (fenamates), including mefenamic acid and meclofenamic acid; enolic acids, including oxicams (piroxicam, tenoxicam), and pyrazolidinediones (phenylbutazone, oxyphenthartazone); and alkanones, including nabumetone. For a more detailed description of the NSAIDs, see Paul A. Insel, *Analgesic-Antipyretic and Anti-inflammatory Agents and Drugs Employed in the Treatment of Gout*, in Goodman & Gilman's *The Pharmacological Basis of Therapeutics* 617-57 (Perry B. Molinoff and Raymond W. Ruddon eds., 9th ed 1996) and Glen R. Hanson, *Analgesic, Antipyretic and Anti-Inflammatory Drugs in Remington: The Science and Practice of Pharmacy Vol II* 1196-1221 (A.R. Gennaro ed. 19th ed. 1995) which are hereby incorporated by reference in their entireties.

Examples of useful Cox-II inhibitors and 5-lipoxygenase inhibitors, as well as combinations thereof, are described in U.S. Patent No. 6,136,839, which is hereby incorporated by reference in its entirety. Examples of useful Cox-II inhibitors include, but are not limited to, rofecoxib and celecoxib.

Examples of useful antimigraine agents include, but are not limited to, alpiropride, dihydroergotamine, dolasetron, ergocornine, ergocorninine, ergocryptine, ergot,

ergotamine, flumedroxone acetate, fonazine, lisuride, lomerizine, methysergide oxetorone, pizotyline, and mixtures thereof.

The other therapeutic agent can also be an agent useful for reducing any potential side effect of a Pyridazinylpiperazine Compounds. For example, the other
5 therapeutic agent can be an antiemetic agent. Examples of useful antiemetic agents include, but are not limited to, metoclopramide, domperidone, prochlorperazine, promethazine, chlorpromazine, trimethobenzamide, odansteron, granisetron, hydroxyzine, acetylleucine monoethanolamine, alizapride, azasetron, benzquinamide, bietanautine, bromopride, buclizine, clebopride, cyclizine, dimenhydrinate, diphenidol, dolasetron, meclizine,
10 methallatal, metopimazine, nabilone, oxypemndyl, pipamazine, scopolamine, sulpiride, tetrahydrocannabinol, thiethylperazine, thioproperazine, tropisetron, and mixtures thereof.

Examples of useful β -adrenergic blockers include, but are not limited to, acebutolol, alprenolol, amosulabol, arotinolol, atenolol, befunolol, betaxolol, bevantolol, bisoprolol, bopindolol, bucumolol, bufetolol, bufuralol, bunitrolol, bupranolol, butidrine
15 hydrochloride, butofilolol, carazolol, carteolol, carvedilol, celiprolol, cetamolol, cloranolol, dilevalol, epanolol, esmolol, indenolol, labetalol, levobunolol, mepindolol, metipranolol, metoprolol, moprolol, nadolol, nadoxolol, nebivalol, nifenalol, nipradilol, oxprenolol, penbutolol, pindolol, practolol, pronethalol, propranolol, sotalol, sulfinalol, talinolol, tertatolol, tilisolol, timolol, toliprolol, and xibenolol.

20 Examples of useful anticonvulsants include, but are not limited to, acetylpheneturide, albutoin, aloxidone, aminoglutethimide, 4-amino-3-hydroxybutyric acid, atrolactamide, beclamide, buramate, calcium bromide, carbamazepine, cinromide, clomethiazole, clonazepam, decimemide, diethadione, dimethadione, doxenitroin, eterobarb, ethadione, ethosuximide, ethotoin, felbamate, fluoresone, gabapentin, 5-hydroxytryptophan,
25 lamotrigine, magnesium bromide, magnesium sulfate, mephenytoin, mephobarbital, metharbital, methetoin, methsuximide, 5-methyl-5-(3-phenanthryl)-hydantoin, 3-methyl-5-phenylhydantoin, narcobarbital, nimetazepam, nitrazepam, oxcarbazepine, paramethadione, phenacemide, phenetharbital, pheneturide, phenobarbital, phensuximide, phenylmethylbarbituric acid, phenytoin, phethenylate sodium, potassium bromide,
30 pregabalin, primidone, progabide, sodium bromide, solanum, strontium bromide, suclofenide, sulthiame, tetrantoin, tiagabine, topiramate, trimethadione, valproic acid, valpromide, vigabatrin, and zonisamide.

Examples of useful antidepressants include, but are not limited to, binedaline, caroxazone, citalopram, dimethazan, fencamine, indalpine, indeloxazine

hydrochloride, nefopam, nomifensine, oxitriptan, oxypertine, paroxetine, sertraline, thiazesim, trazodone, benmoxine, iproclozide, iproniazid, isocarboxazid, nialamide, octamoxin, phenelzine, cotinine, rolicyprine, rolipram, maprotiline, metralindole, mianserin, mirtazepine, adinazolam, amitriptyline, amitriptylinoxide, amoxapine, butriptyline, 5 clomipramine, demexiptiline, desipramine, dibenzepin, dimetacrine, dothiepin, doxepin, fluacizine, imipramine, imipramine N-oxide, iprindole, lofepramine, melitracen, metapramine, nortriptyline, noxiptilin, opipramol, pizotyline, propizepine, protriptyline, quinupramine, tianeptine, trimipramine, adrafinil, benactyzine, bupropion, butacetin, dioxadrol, duloxetine, etoperidone, febarbamate, femoxetine, fentpentadiol, fluoxetine, 10 fluvoxamine, hematoporphyrin, hypericin, levophacetoperane, medifoxamine, milnacipran, minaprine, moclobemide, nefazodone, oxaflazane, piberaline, prolintane, pyrisuccideanol, ritanserin, roxindole, rubidium chloride, sulpiride, tandospirone, thozalinone, tofenacin, toloxatone, tranylcypromine, L-tryptophan, venlafaxine, viloxazine, and zimelidine.

Examples of useful Ca²⁺-channel blockers include, but are not limited to, 15 bepridil, clentiazem, diltiazem, fendiline, gallopamil, mibefradil, prenylamine, semotiadil, terodiline, verapamil, amlodipine, aranidipine, barnidipine, benidipine, cilnidipine, efonidipine, elgodipine, felodipine, isradipine, lacidipine, lercanidipine, manidipine, nicardipine, nifedipine, nilvadipine, nimodipine, nisoldipine, nitrendipine, cinnarizine, flunarizine, lidoflazine, lomerizine, bencyclane, etafenone, fantofarone, and perhexiline.

Examples of useful anticancer agents include, but are not limited to, acivicin, 20 aclarubicin, acodazole hydrochloride, acronine, adozelesin, aldesleukin, altretamine, ambomycin, ametantrone acetate, aminoglutethimide, amsacrine, anastrozole, anthramycin, asparaginase, asperlin, azacitidine, azetepa, azotomycin, batimastat, benzodepa, bicalutamide, bisantrene hydrochloride, bisnafide dimesylate, bizelesin, bleomycin sulfate, brequinar sodium, bropirimine, busulfan, cactinomycin, calusterone, caracemide, 25 carbetimer, carboplatin, carmustine, carubicin hydrochloride, carzelesin, cedefingol, chlorambucil, cirolemycin, cisplatin, cladribine, crisnatol mesylate, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunorubicin hydrochloride, decitabine, dexormaplatin, dezaguanine, dezaguanine mesylate, diaziquone, docetaxel, doxorubicin, doxorubicin hydrochloride, droloxifene, droloxifene citrate, dromostanolone propionate, 30 duazomycin, edatrexate, eflornithine hydrochloride, elsamitrucin, enloplatin, enpromate, epipropidine, epirubicin hydrochloride, erbulozole, esorubicin hydrochloride, estramustine, estramustine phosphate sodium, etanidazole, etoposide, etoposide phosphate, etoprine, fadrozole hydrochloride, fazarabine, fenretinide, floxuridine, fludarabine phosphate, fluorouracil, flurocitabine, fosquidone, fostriecin sodium, gemcitabine, gemcitabine 35

hydrochloride, hydroxyurea, idarubicin hydrochloride, ifosfamide, ilmofofosine, interleukin II (including recombinant interleukin II or rIL2), interferon alfa-2a, interferon alfa-2b, interferon alfa-n1 , interferon alfa-n3, interferon beta-I a, interferon gamma-I b, iproplatin, irinotecan hydrochloride, lanreotide acetate, letrozole, leuprolide acetate, liarozole

5 hydrochloride, lometrexol sodium, lomustine, losoxantrone hydrochloride, masoprocol, maytansine, mechlorethamine hydrochloride, megestrol acetate, melengestrol acetate, melphalan, menogaril, mercaptopurine, methotrexate, methotrexate sodium, metoprine, meturedapa, mitindomide, mitocarcin, mitocromin, mitogillin, mitomalcin, mitomycin, mitosper, mitotane, mitoxantrone hydrochloride, mycophenolic acid, nocodazole,

10 nogalamycin, ormaplatin, oxisuran, paclitaxel, pegaspargase, peliomycin, pentamustine, peplomycin sulfate, perfosfamide, pipobroman, piposulfan, piroxantrone hydrochloride, plicamycin, plomestane, porfimer sodium, porfiromycin, prednimustine, procarbazine hydrochloride, puromycin, puromycin hydrochloride, pyrazofurin, riboprime, rogletimide, safingol, safingol hydrochloride, semustine, simtrazene, sparfosate sodium, sparsomycin,

15 spirogermanium hydrochloride, spiromustine, spiroplatin, streptonigrin, streptozotocin, sulofenur, talisomycin, tecogalan sodium, tegafur, teloxantrone hydrochloride, temoporfin, teniposide, teroxirone, testolactone, thiamiprine, thioguanine, thiotepa, tiazofurin, tirapazamine, toremifene citrate, trestolone acetate, triciribine phosphate, trimetrexate, trimetrexate glucuronate, triptorelin, tubulozole hydrochloride, uracil mustard, uredepa,

20 vapreotide, verteporfin, vinblastine sulfate, vincristine sulfate, vindesine, vindesine sulfate, vinepidine sulfate, vinglycinate sulfate, vinleurosine sulfate, vinorelbine tartrate, vinrosidine sulfate, vinzolidine sulfate, vorozole, zeniplatin, zinostatin, zorubicin hydrochloride.

Examples of other anti-cancer drugs include, but are not limited to,

20-epi-1,25 dihydroxyvitamin D3; 5-ethynyluracil; abiraterone; aclarubicin; acylfulvene;

25 adecypenol; adozelesin; aldesleukin; ALL-TK antagonists; altretamine; ambamustine; amidox; amifostine; aminolevulinic acid; amrubicin; amsacrine; anagrelide; anastrozole; andrographolide; angiogenesis inhibitors; antagonist D; antagonist G; antarelix; anti-dorsalizing morphogenetic protein-1; antiandrogen, prostatic carcinoma; antiestrogen; antineoplaston; antisense oligonucleotides; aphidicolin glycinate; apoptosis gene

30 modulators; apoptosis regulators; apurinic acid; ara-CDP-DL-PTBA; arginine deaminase; asulacrine; atamestane; atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron; azatoxin; azatyrosine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists; benzochlorins; benzoylstauroporine; beta lactam derivatives; beta-aethine; betaclamycin B; betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine;

35 bisnafide; bistratene A; bizelesin; breflate; broprimine; budotitane; buthionine sulfoximine;

calcipotriol; calphostin C; camptothecin derivatives; canarypox IL-2; capecitabine;
 carboxamide-amino-triazole; carboxyamidotriazole; CaRest M3; CARN 700; cartilage
 derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B;
 cetrotorelix; chlorlins; chloroquinoxaline sulfonamide; cicaprost; cis-porphyrin; cladribine;
 5 clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4;
 combretastatin analogue; conagenin; crambescidin 816; crisnatol; cryptophycin 8;
 cryptophycin A derivatives; curacin A; cyclopentantraquinones; cycloplatan; cypemycin;
 cytarabine ocfosfate; cytolytic factor; cytostatin; daclicimab; decitabine; dehydrodidemnin
 B; deslorelin; dexamethasone; dexifosfamide; dexrazoxane; dexverapamil; diaziquone;
 10 didemnin B; didox; diethylnorspermine; dihydro-5-azacytidine; dihydrotaxol, 9-;
 dioxamycin; diphenyl spiromustine; docetaxel; docosanol; dolasetron; doxifluridine;
 droloxifene; dronabinol; duocarmycin SA; ebselen; ecomustine; edelfosine; edrecolomab;
 eflornithine; elemene; emitefur; epirubicin; epristeride; estramustine analogue; estrogen
 agonists; estrogen antagonists; etanidazole; etoposide phosphate; exemestane; fadrozole;
 15 fazarabine; fenretinide; filgrastim; finasteride; flavopiridol; flezelastine; fluasterone;
 fludarabine; fluorodaunorubicin hydrochloride; forfenimex; formestane; fostriecin;
 fotemustine; gadolinium texaphyrin; gallium nitrate; galocitabine; ganirelix; gelatinase
 inhibitors; gemcitabine; glutathione inhibitors; hepsulfam; heregulin; hexamethylene
 bisacetamide; hypericin; ibandronic acid; idarubicin; idoxifene; idramantone; ilmofosine;
 20 ilomastat; imidazoacridones; imiquimod; immunostimulant peptides; insulin-like growth
 factor-1 receptor inhibitor; interferon agonists; interferons; interleukins; iobenguane;
 iododoxorubicin; ipomeanol, 4-; iroplact; irsogladine; isobengazole; isohomohalicondrin B;
 itasetron; jasplakinolide; kahalalide F; lamellarin-N triacetate; lanreotide; leinamycin;
 lenograstim; lentinan sulfate; leptolstatin; letrozole; leukemia inhibiting factor; leukocyte
 25 alpha interferon; leuprolide+estrogen+progesterone; leuprorelin; levamisole; liarozole;
 linear polyamine analogue; lipophilic disaccharide peptide; lipophilic platinum compounds;
 lissoclinamide 7; lobaplatin; lombricine; lometrexol; lonidamine; losoxantrone; lovastatin;
 loxoribine; lurtotecan; lutetium texaphyrin; lysofylline; lytic peptides; maitansine;
 mannostatin A; marimastat; masoprocol; maspin; matrilysin inhibitors; matrix
 30 metalloproteinase inhibitors; menogaril; merbarone; meterelin; methioninase;
 metoclopramide; MIF inhibitor; mifepristone; miltefosine; mirimostim; mismatched double
 stranded RNA; mitoguazone; mitolactol; mitomycin analogues; mitonafide; mitotoxin
 fibroblast growth factor-saporin; mitoxantrone; mofarotene; molgramostim; monoclonal
 antibody, human chorionic gonadotrophin; monophosphoryl lipid A+myobacterium cell
 35 wall sk; mopidamol; multiple drug resistance gene inhibitor; multiple tumor suppressor

1-based therapy; mustard anticancer agent; mycaperoxide B; mycobacterial cell wall
 extract; myriaporone; N-acetyldinaline; N-substituted benzamides; nafarelin; nagrestip;
 naloxone+pentazocine; napavin; naphterpin; nartograstim; nedaplatin; nemorubicin;
 neridronic acid; neutral endopeptidase; nilutamide; nisamycin; nitric oxide modulators;
 5 nitroxide antioxidant; nitrullyn; O6-benzylguanine; octreotide; okicenone; oligonucleotides;
 onapristone; odansteron; oracin; oral cytokine inducer; ormaplatin; osaterone; oxaliplatin;
 oxaunomycin; paclitaxel; paclitaxel analogues; paclitaxel derivatives; palauamine;
 palmitoylrhizoxin; pamidronic acid; panaxytriol; panomifene; parabactin; pazelliptine;
 pegaspargase; peldesine; pentosan polysulfate sodium; pentostatin; pentroazole; perflubron;
 10 perfosfamide; perillyl alcohol; phenazinomycin; phenylacetate; phosphatase inhibitors;
 picibanil; pilocarpine hydrochloride; pirarubicin; piritrexim; placetin A; placetin B;
 plasminogen activator inhibitor; platinum complex; platinum compounds;
 platinum-triamine complex; porfimer sodium; porfiromycin; prednisone; propyl
 bis-acridone; prostaglandin J2; proteasome inhibitors; protein A-based immune modulator;
 15 protein kinase C inhibitor; protein kinase C inhibitors, microalgal; protein tyrosine
 phosphatase inhibitors; purine nucleoside phosphorylase inhibitors; purpurins;
 pyrazoloacridine; pyridoxylated hemoglobin polyoxyethylene conjugate; raf antagonists;
 raltitrexed; ramosetron; ras farnesyl protein transferase inhibitors; ras inhibitors; ras-GAP
 inhibitor; retelliptine demethylated; rhenium Re 186 etidronate; rhizoxin; ribozymes; RII
 20 retinamide; rogletimide; rohitukine; romurtide; roquinimex; rubiginone B1; ruboxyl;
 safingol; saintopin; SarCNU; sarcophytol A; sargramostim; Sdi 1 mimetics; semustine;
 senescence derived inhibitor 1; sense oligonucleotides; signal transduction inhibitors; signal
 transduction modulators; single chain antigen binding protein; sizofiran; sobuzoxane;
 sodium borocaptate; sodium phenylacetate; solverol; somatomedin binding protein;
 25 sonermin; sparfosic acid; spicamycin D; spiromustine; splenopentin; spongistatin 1;
 squalamine; stem cell inhibitor; stem-cell division inhibitors; stipiamide; stromelysin
 inhibitors; sulfinosine; superactive vasoactive intestinal peptide antagonist; suradista;
 suramin; swainsonine; synthetic glycosaminoglycans; tallimustine; tamoxifen methiodide;
 tauromustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium; telomerase inhibitors;
 30 temoporfin; temozolomide; teniposide; tetrachlorodecaoxide; tetrazomine; thaliblastine;
 thiocoraline; thrombopoietin; thrombopoietin mimetic; thymalfasin; thymopoietin receptor
 agonist; thymotrinan; thyroid stimulating hormone; tin ethyl etiopurpurin; tirapazamine;
 titanocene bichloride; topsentin; toremifene; totipotent stem cell factor; translation
 inhibitors; tretinoin; triacetyluridine; triciribine; trimetrexate; triptorelin; tropisetron;
 35 turosteride; tyrosine kinase inhibitors; tyrphostins; UBC inhibitors; ubenimex; urogenital

sinus-derived growth inhibitory factor; urokinase receptor antagonists; vapreotide; variolin B; vector system, erythrocyte gene therapy; velaresol; veramine; verdins; verteporfin; vinorelbine; vinxaltine; vitaxin; vorozole; zanoterone; zeniplatin; zilascorb; and zinostatin stimalamer.

- 5 Examples of useful therapeutic agents for treating or preventing UI include, but are not limited to, propantheline, imipramine, hyoscyamine, oxybutynin, and dicyclomine.

- 10 Examples of useful therapeutic agents for treating or preventing an ulcer include, antacids such as aluminum hydroxide, magnesium hydroxide, sodium bicarbonate, and calcium bicarbonate; sucralfate; bismuth compounds such as bismuth subsalicylate and bismuth subcitrate; H₂ antagonists such as cimetidine, ranitidine, famotidine, and nizatidine; H⁺, K⁺ - ATPase inhibitors such as omeprazole, lansoprazole, and lansoprazole; carbenoxolone; misoprostol; and antibiotics such as tetracycline, metronidazole, tinidazole, clarithromycin, and amoxicillin.

- 15 Examples of useful therapeutic agents for treating or preventing IBD include, but are not limited to, anticholinergic drugs; diphenoxylate; loperamide; deodorized opium tincture; codeine; broad-spectrum antibiotics such as metronidazole; sulfasalazine; olsalazine; mesalamine; prednisone; azathioprine; mercaptopurine; and methotrexate.

- 20 Examples of useful therapeutic agents for treating or preventing IBS include, but are not limited to, propantheline; muscarine receptor antagonists such as pirenzapine, methoctramine, ipratropium, tiotropium, scopolamine, methscopolamine, homatropine, homatropine methylbromide, and methantheline; and antidiarrheal drugs such as diphenoxylate and loperamide.

- 25 Examples of useful therapeutic agents for treating or preventing an addictive disorder include, but are not limited to, methadone, desipramine, amantadine, fluoxetine, buprenorphine, an opiate agonist, 3-phenoxypyridine, levomethadyl acetate hydrochloride, and serotonin antagonists.

- 30 Examples of useful therapeutic agents for treating or preventing Parkinson's disease and parkinsonism include, but are not limited to, carbidopa/levodopa, pergolide, bromocriptine, ropinirole, pramipexole, entacapone, tolcapone, selegiline, amantadine, and trihexyphenidyl hydrochloride.

 Examples of useful therapeutic agents for treating or preventing anxiety include, but are not limited to, benzodiazepines, such as alprazolam, brotizolam,

chlordiazepoxide, clobazam, clonazepam, clorazepate, demoxepam, diazepam, estazolam, flumazenil, flurazepam, halazepam, lorazepam, midazolam, nitrazepam, nordazepam, oxazepam, prazepam, quazepam, temazepam, and triazolam; non-benzodiazepine agents, such as buspirone, gepirone, ipsapirone, tiospirone, zolpicone, zolpidem, and zaleplon;
5 tranquilizers, such as barbituates, *e.g.*, amobarbital, aprobarbital, butabarbital, butalbital, mephobarbital, methohexital, pentobarbital, phenobarbital, secobarbital, and thiopental; and propanediol carbamates, such as meproamate and tybamate.

Examples of useful therapeutic agents for treating or preventing epilepsy include, but are not limited to, carbamazepine, ethosuximide, gabapentin, lamotrigine,
10 phenobarbital, phenytoin, primidone, valproic acid, trimethadione, benzodiazepines, γ -vinyl GABA, acetazolamide, and felbamate.

Examples of useful therapeutic agents for treating or preventing stroke include, but are not limited to, anticoagulants such as heparin, agents that break up clots such as streptokinase or tissue plasminogen activator, agents that reduce swelling such as
15 mannitol or corticosteroids, and acetylsalicylic acid.

Examples of useful therapeutic agents for treating or preventing a seizure include, but are not limited to, carbamazepine, ethosuximide, gabapentin, lamotrigine, phenobarbital, phenytoin, primidone, valproic acid, trimethadione, benzodiazepines, gabapentin, lamotrigine, γ -vinyl GABA, acetazolamide, and felbamate.

20 Examples of useful therapeutic agents for treating or preventing a pruritic condition include, but are not limited to, naltrexone; nalmefene; danazol; tricyclics such as amitriptyline, imipramine, and doxepin; antidepressants such as those given below, menthol; camphor; phenol; pramoxine; capsaicin; tar; steroids; and antihistamines.

Examples of useful therapeutic agents for treating or preventing psychosis
25 include, but are not limited to, phenothiazines such as chlorpromazine hydrochloride, mesoridazine besylate, and thioridazine hydrochloride; thioxanthenes such as chlorprothixene and thiothixene hydrochloride; clozapine; risperidone; olanzapine; quetiapine; quetiapine fumarate; haloperidol; haloperidol decanoate; loxapine succinate; molindone hydrochloride; pimozide; and ziprasidone.

30 Examples of useful therapeutic agents for treating or preventing Huntington's chorea include, but are not limited to, haloperidol and pimozide.

Examples of useful therapeutic agents for treating or preventing ALS include, but are not limited to, baclofen, neurotrophic factors, riluzole, tizanidine, benzodiazepines such as clonazepam and dantrolene.

5 Examples of useful therapeutic agents for treating or preventing cognitive disorders include, but are not limited to, agents for treating or preventing dementia such as tacrine; donepezil; ibuprofen; antipsychotic drugs such as thioridazine and haloperidol; and antidepressant drugs such as those given below.

10 Examples of useful therapeutic agents for treating or preventing a migraine include, but are not limited to, sumatriptan; methysergide; ergotamine; caffeine; and beta-blockers such as propranolol, verapamil, and diltiazem.

15 Examples of useful therapeutic agents for treating, inhibiting, or preventing vomiting include, but are not limited to, 5-HT₃ receptor antagonists such as ondansetron, dolasetron, granisetron, and tropisetron; dopamine receptor antagonists such as prochlorperazine, thiethylperazine, chlorpromazine, metoclopramide, and domperidone; glucocorticoids such as dexamethasone; and benzodiazepines such as lorazepam and alprazolam.

Examples of useful therapeutic agents for treating or preventing dyskinesia include, but are not limited to, reserpine and tetrabenazine.

20 Examples of useful therapeutic agents for treating or preventing depression include, but are not limited to, tricyclic antidepressants such as amitriptyline, amoxapine, bupropion, clomipramine, desipramine, doxepin, imipramine, maprotiline, nefazadone, nortriptyline, protriptyline, trazodone, trimipramine, and venlafaxine; selective serotonin reuptake inhibitors such as fluoxetine, fluvoxamine, paroxetine, and setraline; monoamine oxidase inhibitors such as isocarboxazid, pargyline, phenelzine, and tranylcypromine; and
25 psychostimulants such as dextroamphetamine and methylphenidate.

A Pyridazinylpiperazine Compound and the other therapeutic agent can act additively or, in one embodiment, synergistically. In one embodiment, a Pyridazinylpiperazine Compound is administered concurrently with another therapeutic agent. In one embodiment, a composition comprising an effective amount of a
30 Pyridazinylpiperazine Compound and an effective amount of another therapeutic agent can be administered. Alternatively, a composition comprising an effective amount of a Pyridazinylpiperazine Compound and a different composition comprising an effective amount of another therapeutic agent can be concurrently administered. In another

embodiment, an effective amount of a Pyridazinylpiperazine Compound is administered prior or subsequent to administration of an effective amount of another therapeutic agent. In this embodiment, the Pyridazinylpiperazine Compound is administered while the other therapeutic agent exerts its therapeutic effect, or the other therapeutic agent is administered while the Pyridazinylpiperazine Compound exerts its preventative or therapeutic effect for treating or a Condition.

A composition of the invention is prepared by a method comprising admixing a Pyridazinylpiperazine Compound or a pharmaceutically acceptable salt and a pharmaceutically acceptable carrier or excipient. Admixing can be accomplished using methods well known for admixing a compound (or salt) and a pharmaceutically acceptable carrier or excipient. In one embodiment the Pyridazinylpiperazine Compound or the pharmaceutically acceptable salt of the Compound is present in the composition in an effective amount.

3.8.2 KITS

The invention encompasses kits that can simplify the administration of a Pyridazinylpiperazine Compound to an animal.

A typical kit of the invention comprises a unit dosage form of a Pyridazinylpiperazine Compound. In one embodiment, the unit dosage form is a container, which can be sterile, containing an effective amount of a Pyridazinylpiperazine Compound and a pharmaceutically acceptable carrier or excipient. The kit can further comprise a label or printed instructions instructing the use of the Pyridazinylpiperazine Compound to treat or prevent a Condition. The kit can also further comprise a unit dosage form of another therapeutic agent, for example, a container containing an effective amount of the other therapeutic agent. In one embodiment, the kit comprises a container containing an effective amount of a Pyridazinylpiperazine Compound and an effective amount of another therapeutic agent. Examples of other therapeutic agents include, but are not limited to, those listed above.

Kits of the invention can further comprise a device that is useful for administering the unit dosage forms. Examples of such a device includes, but are not limited to, a syringe, a drip bag, a patch, an inhaler, and an enema bag.

The following examples are set forth to assist in understanding the invention and should not, of course, be construed as specifically limiting the invention described and claimed herein. Such variations of the invention, including the substitution of all

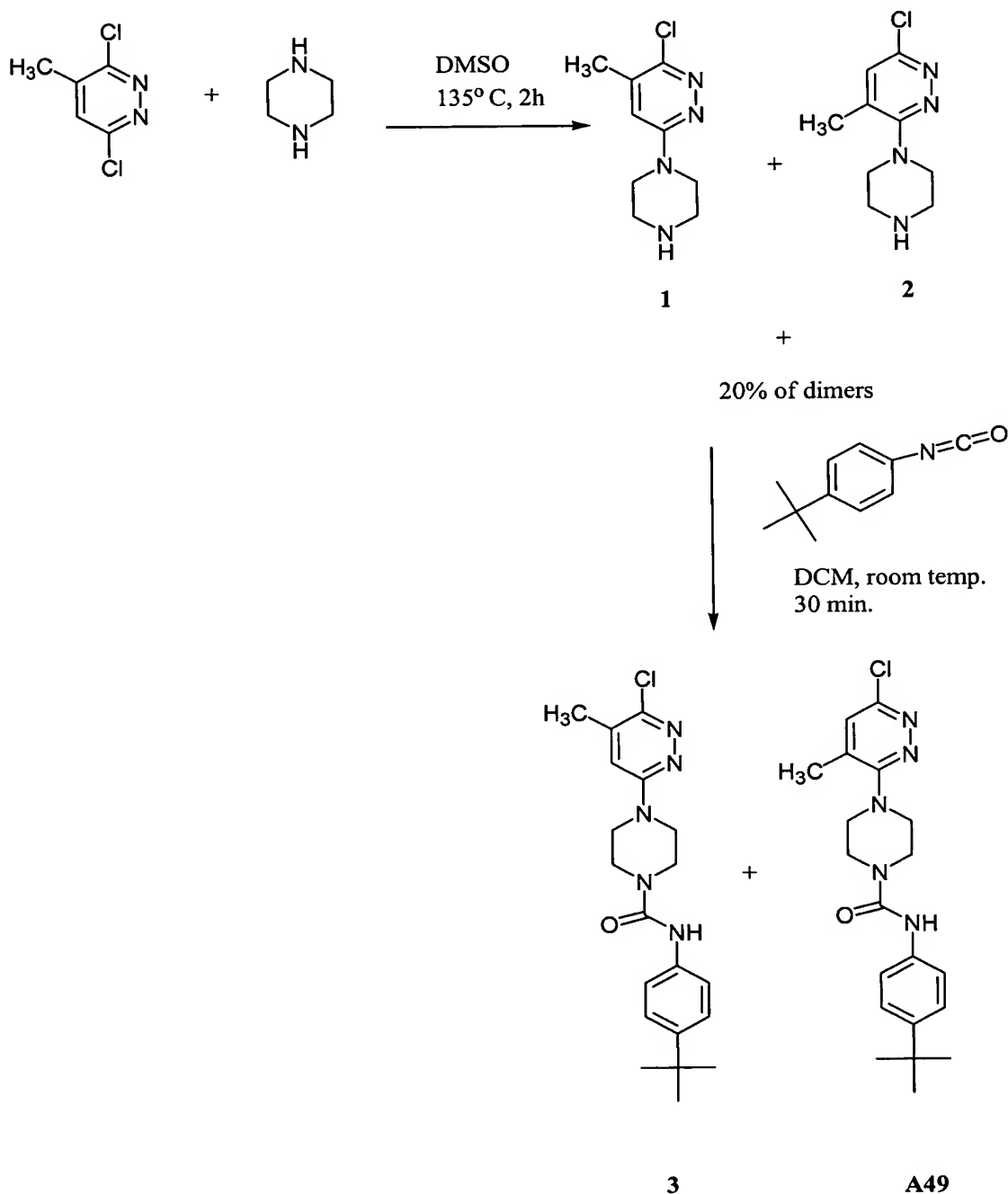
equivalents now known or later developed, which would be within the purview of those skilled in the art, and changes in formulation or minor changes in experimental design, are to be considered to fall within the scope of the invention incorporated herein.

4. EXAMPLES

Examples 1-6 relate to the synthesis of illustrative Pyridazinylpiperazine Compounds.

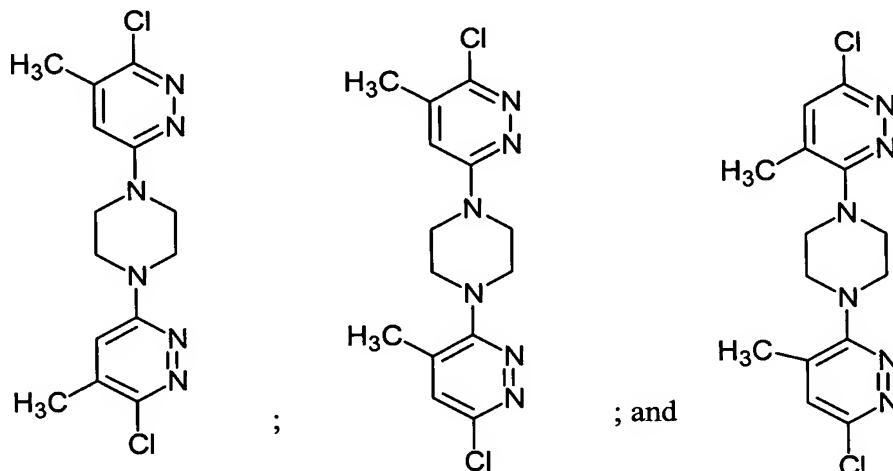
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4.1. **EXAMPLE 1: SYNTHESIS OF 4-(4-METHYL-6-CHLORO-PYRIDAZIN-3-YL)-PIPERAZINE-1-CARBOXYLIC ACID (4-TERT-BUTYL-PHENYL)-AMIDE (COMPOUND A49)**



To a solution of 3,6-dichloro-4-methylpyridazine (150 mg, 0.92 mmol) in 2 mL of DMSO at about 135°C was added piperazine (79 mg, 0.92 mmol). The resulting

solution was stirred at about 135°C for about 1.5 h. The reaction mixture was then cooled to room temperature. Analysis of the reaction mixture using liquid chromatography-mass spectral analysis (LC/MS) showed the formation of Compound 1, Compound 2, and about 20 percent of a mixture of dimers having the the structures shown below:



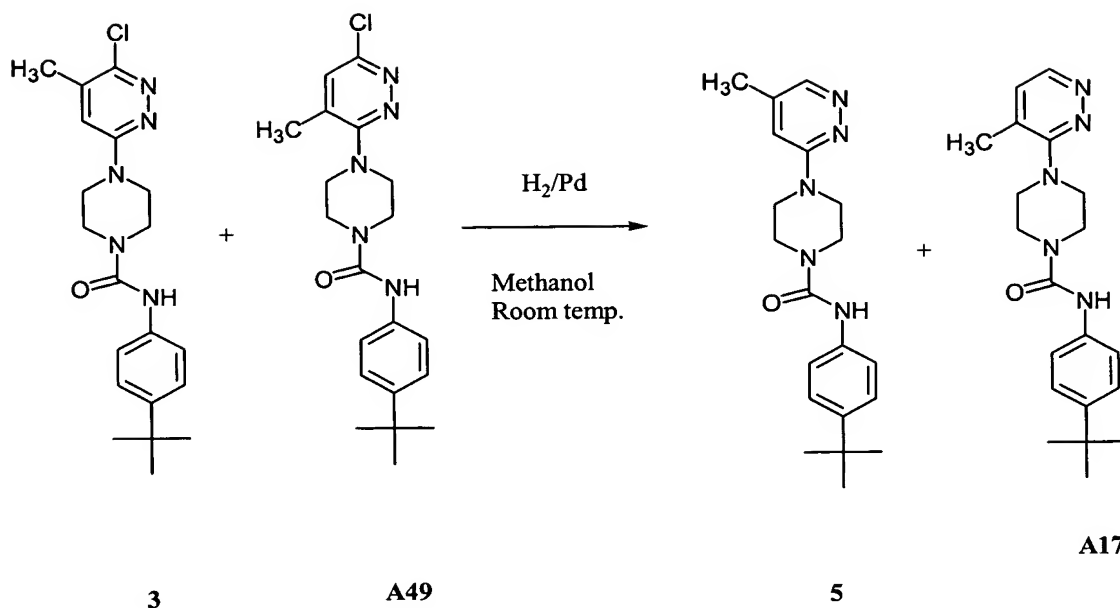
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4-*Tert*-butylphenylisocyanate (0.92 mmol) was added to the cooled reaction mixture and the resulting mixture allowed to stir at room temperature for about 30 min. Analysis of the reaction mixture using LC/MS showed the presence of Compound 3 and Compound A49 in a ratio of 1:5.5. The solvent was removed under reduced pressure to provide a crude mixture of Compound 3 and Compound A49 that was purified by column chromatography using a silica-gel column eluted with 0-100% ethyl acetate/hexane to provide a mixture of Compound 3 and Compound A49. Compound A49 can be isolated from the mixture of Compound 3 and Compound A49 using conventional techniques such as chromatography or recrystallization.

10

15

4.2. EXAMPLE 2: SYNTHESIS OF 4-(4-METHYL-PYRIDAZIN-3-YL)-PIPERAZINE-1-CARBOXYLIC ACID (4-*TERT*-BUTYL-PHENYL)-AMIDE (COMPOUND A17)



A mixture of Compound **3** and Compound **A49**, prepared as described in Example 4.1, was dissolved in methanol and reduced with H₂ over Pd for about 2 h at room temperature. The resulting solution was then purified and separated by column chromatography using a silica-gel column eluted with 0-100% ethyl acetate/hexane to provide

4-(5-Methyl-pyridazin-3-yl)-piperazine-1-carboxylic acid (4-tert-butyl-phenyl)-amide (Compound **5**) and 4-(4-Methyl-pyridazin-3-yl)-piperazine-1-carboxylic acid (4-tert-butyl-phenyl)-amide (Compound **A17**).

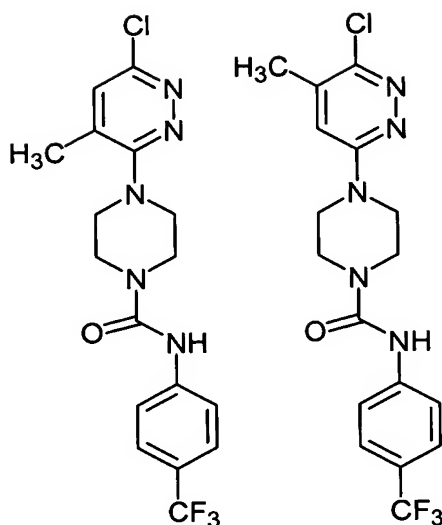
The identity of Compound **5** and Compound **A17** was confirmed using ¹H NMR.

Compound **5**: ¹H NMR (CDCl₃) δ 8.77 (bs, 1H), 7.35-7.25 (m, 4H + CHCl₃), 7.15 (bs, 1H), 6.45 (bs, 1H), 3.73-3.62 (m, 4H), 3.42-3.32 (m, 4H) 2.35 (s, 3H), 1.3 (s, 9H).

Compound **A17**: ¹H NMR (CDCl₃) δ 8.51 (s, 1H), 7.54-7.30 (m, 4H), 6.74 (s, 1H), 6.51 (s, 1H), 3.80-3.69 (m, 8H), 2.30 (s, 3H), 1.32 (s, 9H).

4.3. EXAMPLE 3: SYNTHESIS OF 4-(4-METHYL-6-CHLORO-PYRIDAZIN-3-YL)-PIPERAZINE-1-CARBOXYLIC ACID (4-TRIFLUOROMETHYL-PHENYL)-AMIDE (COMPOUND **A55**)

A mixture of Compound **A55** and Compound **8** was prepared by a procedure analogous to that used to prepare the mixture of Compound **3** and Compound **A49** described in Example 4.1 except that 4-trifluorophenylisocyanate was used in place of 4-tert-butylphenylisocyanate.



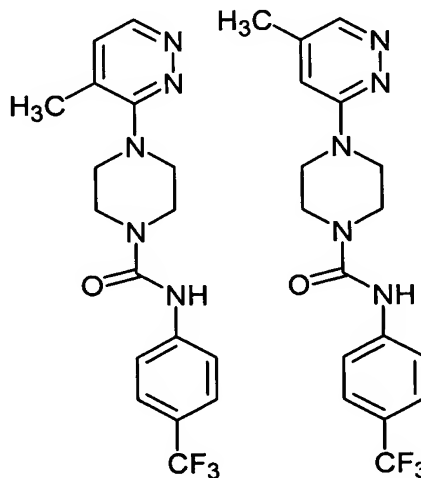
A55

8

Compound **A55** can be isolated from the mixture of Compound **A55** and Compound **8** using conventional techniques such as chromatography or recrystallization.

**4.4. EXAMPLE 4: SYNTHESIS OF
4-(4-METHYL-PYRIDAZIN-3-YL)-PIPERAZINE-1-CARBOXYLIC ACID
(4-TRIFLUOROMETHYL-PHENYL)-AMIDE (COMPOUND A23)**

A mixture of Compound **A55** and Compound **8** was prepared as described in Example 4.3. The mixture of Compound **A55** and Compound **8** was reduced with H₂ over Pd and purified and separated by a procedure analogous to the procedure used to prepare Compound **5** and Compound **A17** described in Example 4.2 to provide Compound **A23** and Compound **10**.



A23

10

The identity of Compound **A23** and Compound **10** was confirmed using ¹H NMR.

Compound **A23**: ^1H NMR (CDCl_3) δ 8.42 (s, 1H), 7.69-7.51 (m, 4H), 7.21 (s, 1H), 3.83-3.65 (m, 4H), 3.44-3.24 (m, 4H), 2.34 (s, 3H).

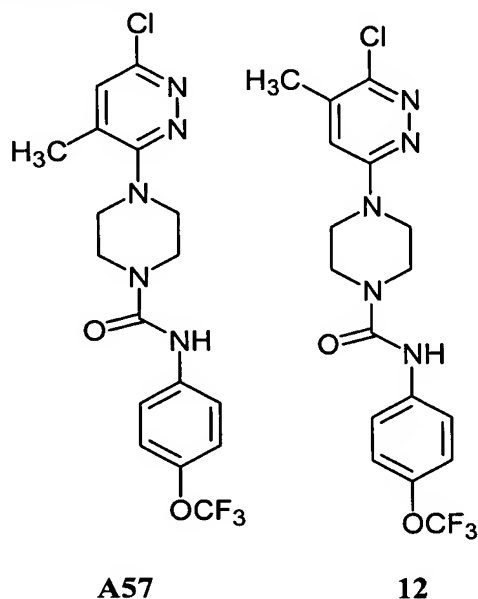
Compound **10**: ^1H NMR (CDCl_3) δ 8.72 (bs, 1H), 7.71-7.53 (m, 4H), 7.42 (bs, 1H), 3.85-3.72 (m, 4H), 3.45-3.34 (m, 4H), 2.42 (s, 3H).

5

4.5. EXAMPLE 5: SYNTHESIS OF 4-(4-METHYL-6-CHLORO-PYRIDAZIN-3-YL)-PIPERAZINE-1-CARBOXYLIC ACID (4-TRIFLUOROMETHOXY-PHENYL)-AMIDE (COMPOUND A57)

A mixture of Compound **A57** and Compound **12** was prepared by a procedure analogous to that used to prepare the mixture of Compound **3** and Compound **A49** described in Example 4.1 except that 4-trifluoromethoxyphenylisocyanate was used in place of 4-*tert*-butylphenylisocyanate.

10



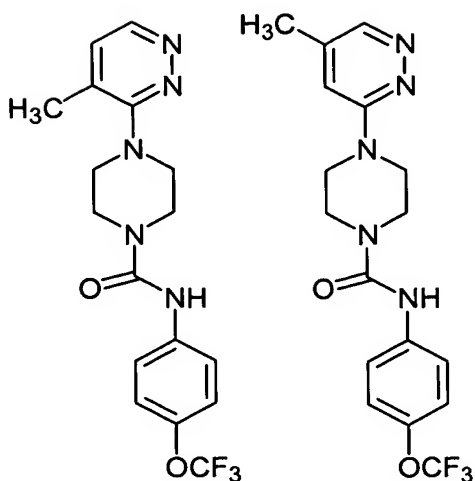
Compound **A57** can be isolated from the mixture of Compound **A57** and Compound **12** using conventional techniques such as chromatography or recrystallization.

15

4.6. EXAMPLE 6: SYNTHESIS OF 4-(4-METHYL-PYRIDAZIN-3-YL)-PIPERAZINE-1-CARBOXYLIC ACID (4-TRIFLUOROMETHOXY-PHENYL)-AMIDE (COMPOUND A25)

A mixture of Compound **A57** and Compound **12** was prepared as described in Example 4.5. The mixture of Compound **A57** and Compound **12** was reduced with H_2 over Pd and purified and separated by a procedure analogous to the procedure used to prepare Compound **5** and Compound **A17** described in Example 4.2 to provide Compound **A25** and Compound **14**.

20



A25

14

The identity of Compound **A25** and Compound **14** was confirmed using ^1H NMR.

Compound **A25**: ^1H NMR (CDCl_3) δ 8.72 (s, 1H), 7.57-7.38 (m, 3H), 7.29-7.12 (m, 2H), 3.84-3.66 (m, 4H), 3.45-3.20 (m, 4H + methanol), 2.49 (s, 3H).

Compound **14**: ^1H NMR (CDCl_3) δ 8.69 (bs, 1H), 7.51-7.46 (m, 4H), 7.21 (bs, 1H), 3.76-3.74 (m, 4H), 3.37-3.32 (m, 4H), 2.35 (s, 3H).

4.7. EXAMPLE 7: BINDING OF TETRAHYDROPIPERIDYL COMPOUNDS TO mGluR5

The following assay can be used to demonstrate Piperidine Compounds that bind to and modulate the activity of mGluR5.

Cell cultures: Primary glial cultures are prepared from cortices of Sprague-Dawley 18 days old embryos. The cortices are dissected and then dissociated by trituration. The resulting cell homogenate is plated onto poly-D-lysine precoated T175 flasks (BIOCOAT, commercially available from Becton Dickinson and Company Inc. of Franklin Lakes, NJ) in Dulbecco's Modified Eagle's Medium ("DMEM," pH 7.4), buffered with 25 mM HEPES, and supplemented with 15% fetal calf serum ("FCS," commercially available from Hyclone Laboratories Inc. of Omaha, NE), and incubated at 37°C and 5% CO_2 . After 24 hours, FCS supplementation is reduced to 10%. On day six, oligodendrocytes and microglia are removed by strongly tapping the sides of the flasks. One day following this purification step, secondary astrocyte cultures are established by subplating onto 96 poly-D-lysine precoated T175 flasks (BIOCOAT) at a density of 65,000 cells/well in DMEM and 10% FCS. After 24 hours, the astrocytes are washed with serum free medium and then cultured in DMEM, without glutamate, supplemented with 0.5% FCS, 20 mM HEPES, 10 ng/mL epidermal growth factor ("EGF"), 1 mM sodium pyruvate, and 1X

penicillin/streptomycin at pH 7.5 for 3 to 5 days at 37°C and 5% CO₂. The procedure allows the expression of the mGluR5 receptor by astrocytes, as demonstrated by S. Miller *et al.*, *J. Neuroscience* **15**(9):6103-6109 (1995).

Assay Protocol: After 3-5 days incubation with EGF, the astrocytes are washed with 127 mM NaCl, 5 mM KCl, 2 mM MgCl₂, 700 mM NaH₂PO₄, 2 mM CaCl₂, 5 mM NaHCO₃, 8 mM HEPES, 10 mM Glucose at pH 7.4 ("Assay Buffer") and loaded with the dye Fluo-4 (commercially available from Molecular Probes Inc. of Eugene, OR) using 0.1 mL of Assay Buffer containing Fluo-4 (3 mM final). After 90 minutes of dye loading, the cells are then washed twice with 0.2 mL Assay Buffer and resuspended in 0.1 mL of Assay Buffer. The plates containing the astrocytes are then transferred to a Fluorometric Imaging Plate reader (commercially available from Molecular Devices Corporation of Sunnyvale, CA) for the assessment of calcium mobilization flux in the presence of glutamate and in the presence or absence of antagonist. After monitoring fluorescence for 15 seconds to establish a baseline, DMSO solutions containing various concentrations of a Pyridazinylpiperazine Compound diluted in Assay Buffer (0.05 mL of 4X dilutions for competition curves) are added to the cell plate and fluorescence is monitored for 2 minutes. 0.05 mL of a 4X glutamate solution (agonist) is then added to each well to provide a final glutamate concentration in each well of 10 mM. Plate fluorescence is then monitored for an additional 60 seconds after agonist addition. The final DMSO concentration in the assay is 1.0%. In each experiment, fluorescence is monitored as a function of time and the data analyzed using Microsoft Excel and GraphPad Prism. Dose-response curves are fit using a non-linear regression to determine IC₅₀ value. In each experiment, each data point is determined two times. The results of this assay will demonstrate that Pyridazinylpiperazine Compounds bind to and modulate the activity of mGluR5.

25 **4.8. EXAMPLE 8: IN VIVO ASSAYS FOR PREVENTION OR TREATMENT OF PAIN**

Test Animals: Each experiment uses rats weighing between 200-260 g at the start of the experiment. The rats are group-housed and have free access to food and water at all times, except prior to oral administration of a Pyridazinylpiperazine Compound when food is removed for 16 hours before dosing. A control group acts as a comparison to rats treated with a Pyridazinylpiperazine Compound. The control group is administered the carrier for the Pyridazinylpiperazine Compound. The volume of carrier administered to the control group is the same as the volume of carrier and Pyridazinylpiperazine Compound administered to the test group.

Acute Pain: To assess the actions of the Pyridazinylpiperazine Compounds for the treatment or prevention of acute pain the rat tail flick test can be used. Rats are placed inside a cotton pouch and the tail exposed to a focused beam of radiant heat at a point 3 cm from the tip using a tail flick unit (Model 7360, commercially available from Ugo Basile of Italy). Tail flick latencies are defined as the interval between the onset of the thermal stimulus and the flick of the tail. Animals not responding within 15 seconds are removed from the tail flick unit and assigned a withdrawal latency of 15 seconds. Tail flick latencies are measured immediately before (pre-treatment) and 1, 3, and 6 hours following administration of a Pyridazinylpiperazine Compound. Data are expressed as tail flick latency(s) and the percentage of the maximal possible effect (% MPE), *i.e.*, 15 seconds, is calculated as follows:

$$\% \text{ MPE} = \frac{[(\text{post administration latency}) - (\text{pre-administration latency})]}{(15 \text{ s pre-administration latency})} \times 100$$

The rat tail flick test is described in F.E. D'Amour *et al.*, "A Method for Determining Loss of Pain Sensation," *J. Pharmacol. Exp. Ther.* 72:74-79 (1941). The results will demonstrate Pyridazinylpiperazine Compounds that are useful for treating or preventing acute pain.

Acute pain can also be assessed by measuring the animal's response to noxious mechanical stimuli by determining the paw withdrawal threshold (PWT), as described below.

Inflammatory Pain: To assess the actions of the Pyridazinylpiperazine Compounds for the treatment or prevention of inflammatory pain the Freund's complete adjuvant (FCA) model of inflammatory pain is used. FCA-induced inflammation of the rat hind paw is associated with the development of persistent inflammatory mechanical hyperalgesia and provides reliable prediction of the anti-hyperalgesic action of clinically useful analgesic drugs (L. Bartho *et al.*, "Involvement of Capsaicin-sensitive Neurones in Hyperalgesia and Enhanced Opioid Antinociception in Inflammation," *Naunyn-Schmiedeberg's Archives of Pharmacology* 342:666-670 (1990)). The left hind paw of each animal is administered a 50 μ L intraplantar injection of 100% FCA. 24 hour post injection, the animal is assessed for response to noxious mechanical stimuli by determining the PWT, as described below. Rats are then administered a single injection of 1, 3, 10 or 30 mg/Kg of either a Pyridazinylpiperazine Compound, 30 mg/Kg indomethacin or carrier. Responses to

noxious mechanical stimuli are then determined 2, 4, 6, and 24 hours post administration. Percentage reversal of hyperalgesia for each animal is defined as:

$$\% \text{ Reversal} = \frac{[(\text{post administration PWT}) - (\text{pre-administration PWT})]}{(\text{Baseline pre-administration PWT})} \times 100$$

The results will demonstrate that Pyridazinylpiperazine Compounds are useful for treating or preventing inflammatory pain.

Neuropathic Pain: To assess the actions of the Pyridazinylpiperazine Compounds for the treatment or prevention of neuropathic pain either the Seltzer model or the Chung model can be used.

In the Seltzer model, the partial sciatic nerve ligation model of neuropathic pain is used to produce neuropathic hyperalgesia in rats (Z. Seltzer *et al.*, "A Novel Behavioral Model of Neuropathic Pain Disorders Produced in Rats by Partial Sciatic Nerve Injury," *Pain* 43:205-218 (1990)). Partial ligation of the left sciatic nerve is performed under isoflurane/O₂ inhalation anaesthesia. Following induction of anesthesia, the left thigh of the rat is shaved and the sciatic nerve exposed at high thigh level through a small incision and is carefully cleared of surrounding connective tissues at a site near the trochanter just distal to the point at which the posterior biceps semitendinosus nerve branches off of the common sciatic nerve. A 7-0 silk suture is inserted into the nerve with a 3/8 curved, reversed-cutting mini-needle and tightly ligated so that the dorsal 1/3 to 1/2 of the nerve thickness is held within the ligature. The wound is closed with a single muscle suture (7-0 silk) and a Michelle clip. Following surgery, the wound area is dusted with antibiotic powder. Sham-treated rats undergo an identical surgical procedure except that the sciatic nerve is not manipulated. Following surgery, animals are weighed and placed on a warm pad until they recover from anesthesia. Animals are then returned to their home cages until behavioral testing begins. The animal is assessed for response to noxious mechanical stimuli by determining PWT, as described below, immediately prior to and 1, 3, and 6 hours after drug administration for both the left rear paw and right rear paw of the animal. Percentage reversal of neuropathic hyperalgesia is defined as:

$$\% \text{ reversal} = 100 - [(\text{right pre-administration PWT} - \text{left post-administration PWT}) / (\text{right pre-administration PWT} - \text{left pre-administration PWT})] \times 100.$$

In the Chung model, the spinal nerve ligation model of neuropathic pain is used to produce mechanical hyperalgesia, thermal hyperalgesia and tactile allodynia in rats. Surgery is performed under isoflurane/O₂ inhalation anaesthesia. Following induction of anaesthesia a 3 cm incision is made and the left paraspinal muscles are separated from the spinous process at the L₄ - S₂ levels. The L₆ transverse process is carefully removed with a pair of small rongeurs to identify visually the L₄ - L₆ spinal nerves. The left L₅ (or L₅ and L₆) spinal nerve(s) is isolated and tightly ligated with silk thread. A complete hemostasis is confirmed and the wound is sutured using non-absorbable sutures, such as nylon sutures or stainless steel staples. Sham-treated rats undergo an identical surgical procedure except that the spinal nerve(s) is not manipulated. Following surgery animals are weighed, administered a subcutaneous (s.c.) injection of saline or ringers lactate, the wound area is dusted with antibiotic powder and they are kept on a warm pad until they recover from the anesthesia. Animals are then be returned to their home cages until behavioral testing begins. The animals are assessed for response to noxious mechanical stimuli by determining PWT, as described below, immediately prior to and 1, 3, and 5 hours after being administered a Pyridazinylpiperazine Compound for both the left rear paw and right rear paw of the animal. The animal can also be assessed for response to noxious thermal stimuli or for tactile allodynia, as described below. The Chung model for neuropathic pain is described in S.H. Kim, "An Experimental Model for Peripheral Neuropathy Produced by Segmental Spinal Nerve Ligation in the Rat," *Pain* 50(3):355-363 (1992). The results will demonstrate that Pyridazinylpiperazine Compounds are useful for treating or preventing neuropathic pain.

Response to Mechanical Stimuli as an Assessment of Mechanical Hyperalgesia:

The paw pressure assay can be used to assess mechanical hyperalgesia. For this assay, hind paw withdrawal thresholds (PWT) to a noxious mechanical stimulus are determined using an analgesymeter (Model 7200, commercially available from Ugo Basile of Italy) as described in C. Stein, "Unilateral Inflammation of the Hindpaw in Rats as a Model of Prolonged Noxious Stimulation: Alterations in Behavior and Nociceptive Thresholds," *Pharmacology Biochemistry and Behavior* 31:451-455 (1988). The maximum weight that can be applied to the hind paw is set at 250 g and the end point is taken as complete withdrawal of the paw. PWT is determined once for each rat at each time point and only the affected (ipsilateral) paw is tested.

Response to Thermal Stimuli as an Assessment of Thermal Hyperalgesia: The plantar test can be used to assess thermal hyperalgesia. For this test, hind paw withdrawal latencies to a noxious thermal stimulus are determined using a plantar test apparatus (commercially available from Ugo Basile of Italy) following the technique described by K.

Hargreaves *et al.*, "A New and Sensitive Method for Measuring Thermal Nociception in Cutaneous Hyperalgesia," *Pain* 32(1):77-88 (1988). The maximum exposure time is set at 32 seconds to avoid tissue damage and any directed paw withdrawal from the heat source is taken as the end point. Three latencies are determined at each time point and averaged.

- 5 Only the affected (ipsilateral) paw is tested.

Assessment of Tactile Allodynia: To assess tactile allodynia, rats are placed in clear, plexiglass compartments with a wire mesh floor and allowed to habituate for a period of at least 15 minutes. After habituation, a series of von Frey monofilaments are presented to the plantar surface of the left (operated) foot of each rat. The series of von Frey
10 monofilaments consists of six monofilaments of increasing diameter, with the smallest diameter fiber presented first. Five trials are conducted with each filament with each trial separated by approximately 2 minutes. Each presentation lasts for a period of 4-8 seconds or until a nociceptive withdrawal behavior is observed. Flinching, paw withdrawal or licking of the paw are considered nociceptive behavioral responses.

15 **4.9. EXAMPLE 9: IN VIVO ASSAYS FOR PREVENTION OR TREATMENT OF ANXIETY**

The elevated plus maze test or the shock-probe burying test can be used to assess the anxiolytic activity of Pyridazinylpiperazine Compounds in rats or mice.

The Elevated Plus Maze Test: The elevated plus maze consists of a platform with 4 arms, two open and two closed (50x10x50 cm enclosed with an open roof). Rats (or mice)
20 are placed in the center of the platform, at the crossroad of the 4 arms, facing one of the closed arms. Time spent in the open arms vs the closed arms and number of open arm entries during the testing period are recorded. This test is conducted prior to drug administration and again after drug administration. Test results are expressed as the mean time spent in open arms and the mean number of entries into open arms. Known anxiolytic
25 drugs increase both the time spent in open arms and number of open arm entries. The elevated plus maze test is described in D. Treit, "Animal Models for the Study of Anti-anxiety Agents: A Review," *Neuroscience & Biobehavioral Reviews* 9(2):203-222 (1985).

The Shock-Probe Burying Test: For the shock-probe burying test the testing apparatus consists of a plexiglass box measuring 40x30x40 cm, evenly covered with
30 approximately 5 cm of bedding material (odor absorbent kitty litter) with a small hole in one end through which a shock probe (6.5 cm long and 0.5 cm in diameter) is inserted. The plexiglass shock probe is helically wrapped with two copper wires through which an electric current is administered. The current is set at 2 mA. Rats are habituated to the testing

apparatus for 30 min on 4 consecutive days without the shock probe in the box. On test day, rats are placed in one corner of the test chamber following drug administration. The probe is not electrified until the rat touches it with its snout or fore paws, at which point the rat receives a brief 2 mA shock. The 15 min testing period begins once the rat receives its first shock and the probe remains electrified for the remainder of the testing period. The shock elicits burying behavior by the rat. Following the first shock, the duration of time the rat spends spraying bedding material toward or over the probe with its snout or fore paws (burying behavior) is measured as well as the number of contact-induced shocks the rat receives from the probe. Known anxiolytic drugs reduce the amount of burying behavior. In addition, an index of the rat's reactivity to each shock is scored on a 4 point scale. The total time spent immobile during the 15 min testing period is used as an index of general activity. The shock-probe burying test is described in D. Treit, 1985, *supra*. The results will demonstrate that Pyridazinylpiperazine Compounds are useful for treating or preventing anxiety.

4.10. EXAMPLE 10: *IN VIVO* ASSAYS FOR PREVENTION OR TREATMENT OF AN ADDICTIVE DISORDER

The condition place preference test or drug self-administration test can be used to assess the ability of Pyridazinylpiperazine Compounds to attenuate the rewarding properties of known drugs of abuse.

The Condition Place Preference Test: The apparatus for the conditioned place preference test consists of two large compartments (45x45x30 cm) made of wood with a plexiglass front wall. These two large compartments are distinctly different. Doors at the back of each large compartment lead to a smaller box (36x18x20 cm) box made of wood, painted grey, with a ceiling of wire mesh. The two large compartments differ in terms of shading (white vs black), level of illumination (the plexiglass door of the white compartment is covered with aluminum foil except for a window of 7x7 cm), texture (the white compartment has a 3 cm thick floor board (40x40 cm) with nine equally spaced 5 cm diameter holes and the black has a wire mesh floor), and olfactory cues (saline in the white compartment and 1 mL of 10% acetic acid in the black compartment). On habituation and testing days, the doors to the small box remain open, giving the rat free access to both large compartments.

The first session that a rat is placed in the apparatus is a habituation session and entrances to the smaller grey compartment remain open giving the rat free access to both large compartments. During habituation, rats generally show no preference for either

compartment. Following habituation, rats are given 6 conditioning sessions. Rats are divided into 4 groups: carrier pre-treatment + carrier (control group), 2-Pyrimidinylpiperazine Compound pre-treatment + carrier, carrier pre-treatment + morphine, 2-Pyrimidinylpiperazine Compound pre-treatment + morphine. During each conditioning session the rat is injected with one of the drug combinations and confined to one compartment for 30 min. On the following day, the rat receives a carrier + carrier treatment and is confined to the other large compartment. Each rat receives three conditioning sessions consisting of 3 drug combination-compartment and 3 carrier-compartment pairings. The order of injections and the drug/compartment pairings are counterbalanced within groups. On the test day, rats are injected prior to testing (30 min to 1 hour) with either morphine or carrier and the rat is placed in the apparatus, the doors to the grey compartment remain open and the rat is allowed to explore the entire apparatus for 20 min. The time spent in each compartment is recorded. Known drugs of abuse increase the time spent in the drug-paired compartment during the testing session. If the Pyridazinylnpiperazine Compound blocks the acquisition of morphine conditioned place preference (reward), there will be no difference in time spent in each side in rats pre-treated with a Pyridazinylnpiperazine Compound and the group will not be different from the group of rats that was given carrier + carrier in both compartments. Data will be analyzed as time spent in each compartment (drug combination-paired vs carrier-paired). Generally, the experiment is repeated with a minimum of 3 doses of a Pyridazinylnpiperazine Compound.

The Drug Self-Administration Test: The apparatus for the drug self-administration test is a standard commercially available operant conditioning chamber. Before drug trials begin rats are trained to press a lever for a food reward. After stable lever pressing behavior is acquired, rats are tested for acquisition of lever pressing for drug reward. Rats are implanted with chronically indwelling jugular catheters for i.v. administration of compounds and are allowed to recover for 7 days before training begins. Experimental sessions are conducted daily for 5 days in 3 hour sessions. Rats are trained to self-administer a known drug of abuse, such as morphine. Rats are then presented with two levers, an “active” lever and an “inactive” lever. Pressing of the active lever results in drug infusion on a fixed ratio 1 (FR1) schedule (*i.e.*, one lever press gives an infusion) followed by a 20 second time out period (signaled by illumination of a light above the levers). Pressing of the inactive lever results in infusion of excipient. Training continues until the total number of morphine infusions stabilizes to within $\pm 10\%$ per session. Trained rats are then used to evaluate the effect of Pyridazinylnpiperazine Compounds pre-treatment on drug self-administration. On test day, rats are pre-treated with a Pyridazinylnpiperazine

Compound or excipient and then are allowed to self-administer drug as usual. If the Pyridazinylpiperazine Compound blocks the rewarding effects of morphine, rats pre-treated with the Pyridazinylpiperazine Compound will show a lower rate of responding compared to their previous rate of responding and compared to excipient pre-treated rats. Data is
5 analyzed as the change in number of drug infusions per testing session (number of infusions during test session – number of infusions during training session). The results of this test will demonstrate that Pyridazinylpiperazine Compounds are useful for treating or preventing an addictive disorder.

4.11. EXAMPLE 11: FUNCTIONAL ASSAY FOR CHARACTERIZING mGluR1 ANTAGONISTIC PROPERTIES

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Functional assays for the characterization of mGluR1 antagonistic properties are well known in the art. For example, the following procedure can be used.

cDNA encoding rat mGluR1a receptor is obtained from, *e.g.*, Prof. S. Nakanishi (Kyoto, Japan). It is transiently transfected into HEK-EBNA cells using a procedure
15 described by Schlaeager *et al.*, *New Dev. New Appl. Anim. Cell Techn.*, Proc. ESACT Meet., 15th (1998), 105-112 and 117-120. [Ca²⁺] measurements are performed on mGluR1a transfected HEK-EBNA cells after incubation of the cells with Fluo-3 AM (0.5 μ M final concentration) for 1 hour at 37°C followed by 4 washes with assay buffer (DMEM supplemented with Hank's salt and 20 mM HEPES. [Ca²⁺] measurements are done using a
20 fluometric imaging plate reader, *e.g.*, FLIPR from Molecular Devices Corporation, La Jolla, CA. 10 μ M glutamate as agonist is used to evaluate the potency of the antagonists.

Increasing concentrations of antagonists are applied to the cells 5 minutes prior to application of the agonist. The inhibition (antagonists) curves are fitted with appropriate software, for example, the four-parameter logistic equation giving IC₅₀ and Hill coefficient
25 using the iterative nonlinear curve fitting software Origin from Microcal Software Inc., Northampton, MA. The results of this assay will demonstrate that Pyridazinylpiperazine Compounds bind to and modulate the activity of mGluR1.

4.12. EXAMPLE 12: BINDING OF PYRIDAZINYLMINOPIPERAZINE COMPOUNDS TO VR1

Methods for assaying compounds capable of inhibiting VR1 are well known
30 to those skilled in the art, for example, those methods disclosed in U.S. Patent No. 6,239,267 to Duckworth *et al.*; U.S. Patent No. 6,406,908 to McIntyre *et al.*; or U.S. Patent No. 6,335,180 to Julius *et al.* The results of these assays will demonstrate that Cyanoiminopiperazine Compounds bind to and modulate the activity of VR1.

Binding of Compound A17 to VR1: Assay Protocol

Human VR1 cloning. Human spinal cord RNA (commercially available from Clontech, Palo Alto, CA) was used. Reverse transcription was conducted on 1.0 μ g total RNA using Thermoscript Reverse Transcriptase (commercially available from Invitrogen, Carlsbad, CA) and oligo dT primers as detailed in its product description. Reverse transcription reactions were incubated at 55°C for 1 h, heat-inactivated at 85°C for 5 min, and RNase H-treated at 37°C for 20 min.

Human VR1 cDNA sequence was obtained by comparison of the human genomic sequence, prior to annotation, to the published rat sequence. Intron sequences were removed and flanking exonic sequences were joined to generate the hypothetical human cDNA. Primers flanking the coding region of human VR1 were designed as follows: forward primer, GAAGATCTTCGCTGGTTGCACACTGGGCCACA; and reverse primer, GAAGATCTTCGGGGACAGTGACGGTTGGATGT.

PCR of VR1 was performed on one tenth of the Reverse transcription reaction mixture using Expand Long Template Polymerase and Expand Buffer 2 in a final volume of 50 μ L according to the manufacturer's instructions (Roche Applied Sciences, Indianapolis, IN). After denaturation at 94°C for 2 min PCR amplification was performed for 25 cycles at 94°C for 15 sec, 58°C for 30 sec, and 68°C for 3 min followed by a final incubation at 72°C for 7 min to complete the amplification. A PCR product of ~2.8 kb was gel-isolated using a 1.0% agarose, Tris-Acetate gel containing 1.6 μ g/mL of crystal violet and purified with a S.N.A.P. UV-Free Gel Purification Kit (commercially available from Invitrogen). The VR1 PCR product was cloned into the pIND/V5-His-TOPO vector (commercially available from Invitrogen) according to the manufacturer's instructions. DNA preparations, restriction enzyme digestions, and preliminary DNA sequencing were performed according to standard protocols. Full-length sequencing confirmed the identity of the human VR1.

Generation of inducible cell lines. Unless noted otherwise, cell culture reagents were purchased from Life Technologies of Rockville, MD. HEK293-EcR cells expressing the ecdysone receptor (commercially available from Invitrogen) were cultured in Growth Medium (Dulbecco's Modified Eagles Medium containing 10% fetal bovine serum (commercially available from HYCLONE, Logan, UT), 1x penicillin/streptomycin, 1x glutamine, 1 mM sodium pyruvate and 400 μ g/mL Zeocin (commercially available from Invitrogen)). The VR1-pIND constructs were transfected into the HEK293-EcR cell line using Fugene transfection reagent (commercially available from Roche Applied Sciences, Basel, Switzerland). After 48 h, cells were transferred to Selection Medium (Growth

Medium containing 300 $\mu\text{g/mL}$ G418 (commercially available from Invitrogen)). Approximately 3 weeks later individual Zeocin/G418 resistant colonies were isolated and expanded. To identify functional clones, multiple colonies were plated into 96-well plates and expression was induced for 48 h using Selection Medium supplemented with 5 μM ponasterone A (“PonA”) (commercially available from Invitrogen). On the day of assay, cells were loaded with Fluo-4 (a calcium-sensitive dye that is commercially available from Molecular Probes, Eugene, OR) and CAP-mediated calcium influx was measured using a Fluorometric Imaging Plate Reader (“FLIPR”) (commercially available from Molecular Devices Corp., Sunnyvale, CA) as described below. Functional clones were re-assayed, expanded, and cryopreserved.

pH-Based Assay. Two days prior to performing this assay, cells were seeded on poly-D-lysine-coated 96-well clear-bottom black plates (commercially available from Becton-Dickinson) at 75,000 cells/well in growth media containing 5 μM PonA (commercially available from Invitrogen) to induce expression. On the day of the assay, the plates were washed with 0.2 mL 1x Hank’s Balanced Salt Solution (commercially available from Life Technologies) containing 1.6 mM CaCl_2 and 20 mM HEPES, pH 7.4 (“wash buffer”), and loaded using 0.1 mL of wash buffer containing Fluo-4 (3 μM final concentration, commercially available from Molecular Probes). After 1 h, the cells were washed twice with 0.2 mL wash buffer and resuspended in 0.05 mL 1x Hank’s Balanced Salt Solution (commercially available from Life Technologies) containing 3.5 mM CaCl_2 and 10 mM Citrate, pH 7.4 (“assay buffer”). Plates were then transferred to a FLIPR (commercially available from Molecular Devices) for assay. Compound A17 was diluted in assay buffer, and 50 μL of the resultant solution were added to the cell plates and the solution monitored for two minutes. The final concentration of Compound A17 ranged from about 50 pM to about 3 μM . Agonist buffer (wash buffer titrated with 1N HCl to provide a solution having a pH of 5.5 when mixed 1:1 with assay buffer) (0.1 mL) was then added to each well, and the plates were incubated for 1 additional minute. Data were collected over the entire time course and analyzed using Excel and Graph Pad Prism. Compound A17 when assayed according to this protocol had an IC_{50} of 220.7 ± 50.5 nM ($n + 3$).

Capsaicin-based Assay. Two days prior to performing this assay, cells were seeded in poly-D-lysine-coated 96-well clear-bottom black plates (50,000 cells/well) in growth media containing 5 μM PonA (commercially available from Invitrogen) to induce expression. On the day of the assay, the plates were washed with 0.2 mL 1x Hank's

Balanced Salt Solution (commercially available from Life Technologies) containing 1 mM CaCl₂ and 20 mM HEPES, pH 7.4, and cells were loaded using 0.1 mL of wash buffer containing Fluo-4 (3 μM final). After one hour, the cells were washed twice with 0.2 mL of wash buffer and resuspended in 0.1 mL of wash buffer. The plates were transferred to a
5 FLIPR (commercially available from Molecular Devices) for assay. 50 μL of Compound A17 diluted with assay buffer were added to the cell plates and incubated for 2 min.. The final concentration of Compound A17 ranged from about 50 pM to about 3 μM. Human VR1 was activated by the addition of 50 μL of capsaicin (400 nM), and the plates were incubated for an additional 3 min. Data were collected over the entire time course and
10 analyzed using Excel and GraphPad Prism. Compound A17 when assayed according to this protocol had an IC₅₀ of 47.2 ± 9.9 nM (n + 3).

The results of the pH-based assay and the capsaicin-based assay demonstrate that Compound A17, an illustrative Pyridazinylpiperazine Compound, binds to and modulates the activity of human VR1.

15 The present invention is not to be limited in scope by the specific embodiments disclosed in the examples which are intended as illustrations of a few aspects of the invention and any embodiments that are functionally equivalent are within the scope of this invention. Indeed, various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art and are intended to fall
20 within the scope of the appended claims.

A number of references have been cited, the entire disclosures of which are incorporated herein by reference.